Jan Delaval Please

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6/8/20

SEARCH REQUEST FORM

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Date: 3/4/02 — Phone: 305-3910 — Art Unit: 1616

Jacques Paris et al.

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Please search for method of ~~contraception~~ by nomegestrol and/or an ester and estradiol or an ester.

nomegestrol is also called ~~progestagen~~ estradiol - - - estrogen =

gestogen + estrogen combination for contraception

Species - Nomegasterol acetate + estradiol

Please see attached sheet.

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Thank you

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- ___ DARC/Questel
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=> fil embase
FILE 'EMBASE' ENTERED AT 14:15:38 ON 15 MAR 2002
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 FILE COVERS 1974 TO 14 Mar 2002 (20020314/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d all tot

L50  ANSWER 1 OF 2  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN   93130379  EMBASE
DN   1993130379
TI   [Progestational contraception: Advantages].
       CONTRACEPTION MACROPROGESTATIVE: AVANTAGES.
AU   Jamin C.
CS   CEGOOP, CMC Foch,Suresnes, France
SO   Contraception Fertilite Sexualite, (1993) 21/2 (123-128).
     ISSN: 1157-8181  CODEN: CFSXAE
CY   France
DT   Journal; (Short Survey)
FS   010     Obstetrics and Gynecology
     030     Pharmacology
     037     Drug Literature Index
LA   French
SL   English; French
AB   In spite of the nearly total effectiveness of classic estrogen-progestogen
     oral contraception and its good overall tolerance, in a not
     inconsiderable number of situations yet, it is not possible to resort to
     it. These situations are the following: high blood pressure, hyperlipemia,
     diabetes, minor mastopathy, premenstrual tension either spontaneous or
     under estroprogestogen therapy. Macroprogestational contraception
     using either pregnanes (chlormadinone acetate) or norpregnanes,
     promegestone, nomegestrol acetate, can be then the
     right solution. Clinical and metabolic tolerance is excellent. In the
     occurence of hypoestrogeny symptoms, a combination of nomegestrol
     acetate-estradiol 17.beta., transdermally administered,
     has given top results in a preliminary study.
CT   Medical Descriptors:
       *contraception
       *oral contraception
     adult
     diabetes mellitus
     female
     human
     hypertension
     lipid metabolism
     major clinical study
     short survey
     transdermal drug administration
     Drug Descriptors:
       *chlormadinone acetate: AD, drug administration
       *estradiol: CB, drug combination
       *estradiol: AD, drug administration
       *ethinylestradiol: AD, drug administration
       *nomegestrol acetate: CB, drug combination
       *nomegestrol acetate: AD, drug administration
       *promegestone: AD, drug administration
RN   (chlormadinone acetate) 302-22-7, 39864-38-5; (estradiol)
     50-28-2; (ethinylestradiol) 57-63-6; (nomegestrol
     acetate) 58652-20-3; (promegestone) 34184-77-5
CN   Lutenyl; Estraderm
```

L50 ANSWER 2 OF 2 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 92230699 EMBASE
DN **1992230699**
TI [Female **contraception** by a normal dose progestogen in patients over the 40 years of age. Possible association of **nomegestrol acetate**/17.beta.-**estradiol** by percutaneous route].
LA **CONTRACEPTION** FEMININE PAR PROGESTATIF NORMODOSE APRES 40 ANS. POSSIBILITIE D'ASSOCIATION ACETATE DE **NOMEGESTROL** - 17-BETA-**ESTRADIOL** PAR VOIE CUTANEE.
AU Jamin C.
CS 169 Bd. Haussmann,75008 Paris, France
SO Revue Francaise de Gynecologie et d'Obstetrique, (1992) 87/6 (370-376).
ISSN: 0035-290X CODEN: RFGOAO
CY France
DT Journal; General Review
FS 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
LA French
SL French; English
AB Although fertility declines with age, the use of an effective **contraceptive** remains necessary in women over 40. Endocrine disorders, which are common in this age group, may also often require control. Conventional estroprogestogens, even those of the latest generation, cannot be used in women with a high cardiovascular risk, since age cannot be totally excluded as a possible risk factor. The **contraceptive** use of derivatives of 17-hydroxyprogesterone and 19-norprogesterone offer a promising alternative, despite the absence of any exhaustive investigation particularly in situations in which the blood level of **estradiol** has to be reduced. There are, however, some women who respond to this Type of **contraception** by menstrual cycle irregularities, and sometimes by low blood levels of **estradiol**, regardless of the drug used. A preliminary study is described in which 5 mg of **nomegestrol acetate** was combined with 17-.beta.-**estradiol** by transcutaneous route and which has so-far demonstrated sustained **contraceptive** efficacy as well as excellent clinical and metabolic safety.
CT Medical Descriptors:
***contraception**
adult
female
human
oral drug administration
priority journal
review
transdermal drug administration
Drug Descriptors:
***contraceptive agent**
***estradiol: CB, drug combination**
***estrogen**
***gestagen**
***nomegestrol acetate: CB, drug combination**
chlormadinone
chlormadinone acetate
promegestone
RN (**estradiol**) **50-28-2**; (**nomegestrol acetate**) **58652-20-3**; (chlormadinone) 1961-77-9; (chlormadinone acetate) 302-22-7, 39864-38-5; (promegestone) 34184-77-5
CN **Lutenyl**; Surgestone; Luteran; Estraderm tts

=> fil medline
FILE 'MEDLINE' ENTERED AT 14:33:39 ON 15 MAR 2002

FILE LAST UPDATED: 14 MAR 2002 (20020314/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d all tot

L83 ANSWER 1 OF 5 MEDLINE
AN **1999135052** MEDLINE
DN **99135052** PubMed ID: **9949893**
TI [Biological and clinical safety of **nomegestrol acetate** administered alone then associated in inverse sequence with transdermal 17 beta **estradiol**, in women at risk of dyslipoproteinemia type IIa].
Tolerance biologique et clinique du **Nomegestrol acetate** , administre seul puis associe en sequentiel inverse au 17 beta **estradiol** cutane, chez des femmes a risque presentant une dyslipoproteinemie de type IIa.
AU Zartarian M; Chevallier T; Micheletti M C; Leber C; Jamin C
CS Service d'Endocrinologie, Reproduction, Diabetologie, Hopital de l'Archet I, Nice.
SO ANNALES D ENDOCRINOLOGIE, (1998 Dec) 59 (5) 411-6.
Journal code: 54O; 0116744. ISSN: 0003-4266.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 199903
ED Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990302
AB In this study including 26 patients with dyslipoproteinemia classified IIa, we evaluated biochemical and clinical safety of **Nomegestrol acetate** (**Lutenyl**) used for its antigonadotrophin property. It was administered alone, during 3 cycles at the dose of 5 mg/d for 21 days by cycle and then it was associated (at the same sequence and dose), without any wash out, for the next 6 cycles, with a 17 beta **estradiol** patch (Estraderm TTS 50), 50 micrograms/d from the 11th to the 21st day of each cycle. **Nomegestrol acetate**, alone, had no significant effect on glycemia, antithrombin III, triglycerides, total cholesterol, apoprotein A1, and LpA1 values compared to those at baseline but apoprotein B and Lp (a) values tended to decrease slightly. Serum progesterone levels were collapsed, and FSH values were low. Weight and blood pressure remained constant. Adding 17 beta **estradiol** enabled to significantly decrease and normalize the apoprotein B values after the first 3 cycles compared to the baseline values, then these values remained constant during the next 3 cycles. There was no effect on the other parameters (except for a significant increase in plasmatic **estradiol** values) on the antigonadotrophin property of **Nomegestrol acetate**, nor on weight and blood pressure which remained constant. Moreover, we observed an important decrease in the rate of amenorrheic cycles compared to those with

Nomegestrol acetate alone.
CT Check Tags: Female; Human
Administration, Cutaneous
Adolescence
Adult
Blood Pressure
***Contraceptives, Oral, Sequential: AD, administration & dosage**
***Estradiol: AD, administration & dosage**
*Hypercholesterolemia, Familial: CO, complications
Middle Age
*Norpregnadienes: AD, administration & dosage
*Progestational Hormones, Synthetic: AD, administration & dosage
RN **50-28-2 (Estradiol); 58652-20-3 (TX 066)**
CN 0 (**Contraceptives, Oral, Sequential**); 0 (Norpregnadienes); 0 (Progestational Hormones, Synthetic)

L83 ANSWER 2 OF 5 MEDLINE
AN **1999039971** MEDLINE
DN **99039971** PubMed ID: **9822518**
TI **Coadministration** of **nomegestrol acetate** does not diminish the beneficial effects of **estradiol** on coronary artery dilator responses in nonhuman primates (Macaca fascicularis).
AU Williams J K; Cline J M; Honore E K; Delansorne R; Paris J
CS Department of Comparative Medicine of Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.
SO AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1998 Nov) 179 (5) 1288-94. Journal code: 3NI; 0370476. ISSN: 0002-9378.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981223
AB OBJECTIVE: Our purpose was to examine the effect of **coadministered nomegestrol acetate** on **estradiol**-induced dilator responses of coronary arteries. STUDY DESIGN: In this prospective randomized trial, ovariectomized monkeys were fed a moderately atherogenic diet for 3 months while being treated with (1) no hormone replacement (control, n = 12), (2) **estradiol** (1.5 mg/d equivalent) added to the diet (n = 12), or (3) **estradiol** (1.5 mg/d equivalent) **plus nomegestrol acetate** (3.75 mg/d equivalent) (n = 12) added to the diet. Effects of treatment were measured with analysis of variance. Post hoc analyses were done by multiple comparison tests with Bonferroni corrections. RESULTS: Constrictor responses of epicardial coronary arteries (measured with quantitative angiography) and decreased coronary blood velocity (measured with Doppler ultrasonography) to acetylcholine (10(-6) mol/L) were less in the **estradiol**-treated monkeys (with or without cotreatment with **nomegestrol acetate**) than in the untreated monkeys (P <.05). Typical estrogenic responses were induced by **estradiol** in the endometrium (ie, increased proliferation [Ki-67 expression] [P <.04] and increased hormone receptor expression). These effects were antagonized by **nomegestrol acetate**. CONCLUSIONS: Although **nomegestrol acetate** has typical progestin-like effects on the uterus, it does not diminish the beneficial effects of estrogen on acetylcholine-induced dilator responses of coronary arteries.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Acetylcholine: PD, pharmacology
Blood Flow Velocity: DE, drug effects
Coronary Angiography
Coronary Circulation: DE, drug effects
*Coronary Vessels: DE, drug effects
Coronary Vessels: US, ultrasonography
Drug Combinations

***Estradiol: PD, pharmacology**
Macaca fascicularis
*Norpregnadienes: PD, pharmacology
Ovariectomy
Prospective Studies
Vasoconstriction: DE, drug effects
*Vasodilation: DE, drug effects
Vasodilator Agents: PD, pharmacology
RN **50-28-2 (Estradiol)**; 51-84-3 (Acetylcholine); **58652-20-3 (TX 066)**
CN 0 (Drug **Combinations**); 0 (Norpregnadienes); 0 (Vasodilator Agents)

L83 ANSWER 3 OF 5 MEDLINE
AN **96148040** MEDLINE
DN **96148040** PubMed ID: **8571051**
TI [Pharmacology of oral **contraceptives**].
Pharmacologie des **contraceptifs** oraux.
AU Sitruk-Ware R
CS Service d'endocrinologie Hopital, Saint-Antoine, Paris.
SO REVUE DU PRATICIEN, (1995 Dec 1) 45 (19) 2401-6.
Journal code: T1D; 0404334. ISSN: 0035-2640.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS F
EM 199603
ED Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960307
AB Oral **contraceptives** include two types of steroids; ethinyl-**estradiol** as the main estrogenic component which dose vary from 20 to 50 micrograms per tablet (mostly 30 to 35 micrograms) and progestins essentially derivatives of 19 nortestosterone. Derivatives of 19 norprogesterone such as **nomegestrol acetate** or ST 1435 are not used as oral **contraceptives** but are being evaluated through parenteral administration, e.g. implants or transdermal systems. The assessment of the pharmacological properties of these progestins indicate a high antigonadotropic and a high antiestrogenic properties for levonorgestrel and for the newer gestagens as well. Therefore very low doses are being used in the current oral **contraceptives**. However, there is a lower margin of security with the low dose **contraceptives** than with previous standard **combinations** and especially when **concomitant** medications are ingested such as enzyme-inducing agents. Selection of **contraceptive** methods should be discussed when specific co-medications are necessary.
CT Check Tags: Female; Human
Contraceptives, Oral, Synthetic: CL, classification
***Contraceptives, Oral, Synthetic: PD, pharmacology**
Steroids: AD, administration & dosage
Steroids: ME, metabolism
Steroids: PD, pharmacology
CN 0 (**Contraceptives**, Oral, Synthetic); 0 (Steroids)

L83 ANSWER 4 OF 5 MEDLINE
AN **95039166** MEDLINE
DN **95039166** PubMed ID: **7524930**
TI [High-dose progestational **contraception**: advantages].
Contraception macroprogestative: avantages.
AU Jamin C
SO CONTRACEPTION, FERTILITE, SEXUALITE, (1993 Feb) 21 (2) 123-8.
Journal code: BUD; 9314045. ISSN: 1165-1083.
CY France
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA French

FS Priority Journals
EM 199412
ED Entered STN: 19950110
Last Updated on STN: 20000303
Entered Medline: 19941209
AB In spite of the nearly total effectiveness of classic estrogen-progestogen oral **contraception** and its good overall tolerance, in a not inconsiderable number of situations yet, it is not possible to resort to it. These situations are the following: high blood pressure, hyperlipemia, diabetes, minor mastopathy, premenstrual tension either spontaneous or under estroprogestogen therapy. Macroprogestational **contraception** using either pregnanes (chlormadinone acetate) or nor-pregnanes, promegestone, **nomegestrol acetate**, can be then the right solution. Clinical and metabolic tolerance is excellent. In the occurrence of hypoestrogeny symptoms, a **combination** of **nomegestrol acetate-estradiol** 17 beta, transdermally administered, has given top results in a preliminary study.
CT Check Tags: Comparative Study; Female; Human
Administration, Cutaneous
Adult
Chlormadinone Acetate: ME, metabolism
Chlormadinone Acetate: PD, pharmacology
***Chlormadinone Acetate: TU, therapeutic use**
Contraceptives, Oral, Combined: ME, metabolism
Contraceptives, Oral, Combined: PD, pharmacology
Contraceptives, Oral, Combined: TU, therapeutic use
Estradiol: BL, blood
Estradiol: ME, metabolism
Estradiol: PD, pharmacology
Estradiol: TU, therapeutic use
Incidence
Menstruation Disturbances: CI, chemically induced
Menstruation Disturbances: EP, epidemiology
Norpregnadienes: ME, metabolism
Norpregnadienes: PD, pharmacology
*Norpregnadienes: TU, therapeutic use
Progestational Hormones, Synthetic: ME, metabolism
Progestational Hormones, Synthetic: PD, pharmacology
*Progestational Hormones, Synthetic: TU, therapeutic use
Promegestone: ME, metabolism
Promegestone: PD, pharmacology
*Promegestone: TU, therapeutic use
RN 302-22-7 (Chlormadinone Acetate); 34184-77-5 (Promegestone); **50-28-2 (Estradiol); 58652-20-3 (TX 066)**
CN 0 (**Contraceptives**, Oral, **Combined**); 0 (Norpregnadienes); 0 (Progestational Hormones, Synthetic)

L83 ANSWER 5 OF 5 MEDLINE
AN **92335763** MEDLINE
DN **92335763** PubMed ID: **1378646**
TI [Female **contraception** by a normal dose progestogen after 40 years of age. Possible association of **nomegestrol**--17-beta-**estradiol** acetate by percutaneous route].
La **contraception** feminine par progestatif normodose apres 40 ans. Possibilite d'association acetate de **nomegestrol**--17-beta-**estradiol** par voie cutanee.
AU Jamin C
CS Service de Gynecologie-Obstetrique, Centre Medico-Chirurgical Foch, Suresnes.
SO REVUE FRANCAISE DE GYNECOLOGIE ET D OBSTETRIQUE, (1992 Jun) 87 (6) 370-6.
Journal code: SOH; 0411346. ISSN: 0035-290X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 199208

ED Entered STN: 19920904
Last Updated on STN: 20000303
Entered Medline: 19920820
AB Although fertility declines with age, the use of an effective **contraceptive** remains necessary in women over 40. Endocrine disorders, which are common in this age group, may also often require control. Conventional estroprogestogens, even those of the latest generation, cannot be used in women with a high cardiovascular risk, since age cannot be totally excluded as a possible risk factor. The **contraceptive** use of derivatives of 17-hydroxyprogesterone and 19-norprogesterone offer a promising alternative, despite the absence of any exhaustive investigation particularly in situations in which the blood level of **estradiol** has to be reduced. There are, however, some women who respond to this type of **contraception** by menstrual cycle irregularities, and sometimes by low blood levels of **estradiol**, regardless of the drug used. A preliminary study is described in which 5 mg of **nomegestrol acetate** was **combined** with 17-beta-**estradiol** by transcutaneous route and which has so-far demonstrated sustained **contraceptive** efficacy as well as excellent clinical and metabolic safety.
CT Check Tags: Comparative Study; Female; Human
Administration, Cutaneous
Adult
Age Factors
Chlormadinone Acetate: AE, adverse effects
***Contraceptive Agents, Female**
***Estradiol: AD, administration & dosage**
Estradiol: AE, adverse effects
Megestrol: AD, administration & dosage
Megestrol: AE, adverse effects
***Megestrol: AA, analogs & derivatives**
Menstruation Disturbances: CI, chemically induced
*Progestational Hormones, Synthetic: AD, administration & dosage
Progestational Hormones, Synthetic: AE, adverse effects
Promegestone: AE, adverse effects
RN 302-22-7 (Chlormadinone Acetate); 34184-77-5 (Promegestone); 3562-63-8 (Megestrol); **50-28-2 (Estradiol); 58691-88-6 (nomegestrol)**
CN 0 (**Contraceptive** Agents, Female); 0 (Progestational Hormones, Synthetic)

=> fil wpix
FILE 'WPIX' ENTERED AT 14:42:35 ON 15 MAR 2002
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FILE LAST UPDATED: 13 MAR 2002 <20020313/UP>
MOST RECENT DERWENT UPDATE 200217 <200217/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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=> d all abeq tech tot

L121 ANSWER 1 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2002-130566 [17] WPIX

DNC C2002-040086
TI Oral **contraceptive** starter kit for ameliorating the problem of breakthrough bleeding and spotting comprises at least two packs comprising an **estrogen** and progestin.
DC B01 B07
IN GRUBB, G S
PA (AMHP) AMERICAN HOME PROD CORP
CYC 96
PI WO 2001093848 A2 20011213 (200217)* EN 13p A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
US 2002010167 A1 20020124 (200217) A61K031-56
ADT WO 2001093848 A2 WO 2001-US18142 20010605; US 2002010167 A1 Provisional US 2000-210310P 20000608, US 2001-872250 20010601
PRAI US 2000-210310P 20000608; US 2001-872250 20010601
IC ICM A61K031-00; A61K031-56
ICS A61K031-57
AB WO 200193848 A UPAB: 20020313
NOVELTY - An oral **contraceptive** starter kit comprises at least two cycle packs of oral **contraceptives** comprising **estrogen** (I) and a progestin (II). The kit has a first and a last cycle pack. The first cycle pack comprises (I) and (II) greater than the last cycle pack.
USE - For ameliorating the problem of breakthrough bleeding and spotting associated with lowest dose **estrogen contraceptives**.
ADVANTAGE - The kit gradually decreases the dose of **estrogen** over a number of cycles and thus decreases incidences of breakthrough bleeding and spotting that are often associated the lose-dose **estrogen contraceptives**.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B01-A02; B01-C03; B01-C04; B01-C05; B01-C06; **B14-P01B**
TECH UPTX: 20020313
TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred Kit: The cycle packs are packaged in individual units and multiple cycle packs are packaged together as a single unit. The last cycle pack provides a daily dosage of (I) equivalent to 20 microg/dosage unit. The dosage of (I) and (II) in the first cycle pack is greater than in subsequent cycle packs. Also, the dosage of (I) and (II) in the penultimate cycle pack is greater than that of in the last cycle pack. The last cycle pack comprises lowest dosage of (I) and (II). The kit further comprises written instructions describing the order of use of the cycle packs.
Preferred Components: The **estrogen** is **ethinylestradiol**. The progestin is trimegestone, **nomegestrol**, norgestrel, levonorgestrol, cyproterone acetate, 3-ketodesogestrel, desogestrel, gestodene, drospirenone, medroxy progesterone acetate, megestrol acetate, norgestimate, 17B diacetyl norgestimate, osaterone, norethindrone, norethindrone acetate, lynestrenol, norethynodrel or ethynodiol diacetate (preferably levonorgestrel, norethindrone, norethindrone acetate, gestodene or norgestimate).

L121 ANSWER 2 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-335679 [35] WPIX
CR 2001-308583 [31]
DNC C2001-103673
TI Hormonal composition for treating menopausal **estrogen** deficiency, osteoporosis and cardiovascular disease, comprises combination of **estrogen** and **progestagen** derived from 19-norprogesterone.
DC B01

IN **PARIS, J; THOMAS, J**
PA (PARI-I) PARIS J; (SOTH) **THERAMEX LAB SA**; (THOM-I) THOMAS J
CYC 18
PI WO 2001030356 A1 20010503 (200135)* FR 31p A61K031-57
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
ADT WO 2001030356 A1 WO 1999-FR2588 19991025
PRAI WO 1999-FR2588 19991025
IC ICM A61K031-57
ICS A61P005-30
AB WO 200130356 A UPAB: 20010625
NOVELTY - Hormonal compositions (A) comprise an orally administered **estrogen-progestagen** combination, allowing the simultaneous administration of an **estrogen** (I) at 0.3-3 mg and a **progestagen** (II) derived from 19-norprogesterone at 0.3-1.5 mg, (I) and (II) being associated or mixed with excipient(s).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the production of (A), by combining (I), (II) and excipient(s).
ACTIVITY - Osteopathic; cardiant; vasotropic.
In tests in menopausal women using 1.5 mg per day of **estradiol** in combination with various doses of **nomegestrol acetate** for 6 months, there was no significant difference in endometrial thickness between groups treated with 0.625, 1.25, 2.5 or 65 mg per day of **nomegestrol acetate**.
MECHANISM OF ACTION - None given.
USE - (A) is specifically used for treating **estrogen** deficiency, preventing osteoporosis and preventing cardiovascular diseases in menopausal women, by continuous or intermittent administration (all claimed). More generally (A) can be used for treating all types of **estrogen** deficiency in women.
ADVANTAGE - Functional disorders caused by menopausal **hypoestrogenia** are controlled while maintaining atrophy of the endometrium and preventing genital bleeding. The required therapeutic effects are obtained using markedly lower doses of (II) than those in related prior art compositions (see FR2754179), so that safety is improved.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B01-A02; B01-A03; B01-C04; B14-D01B; B14-F01; B14-N01
TECH UPTX: 20010625
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (I) is 17beta-**estradiol** or its ester (specifically the valerate) or an equine conjugated **estrogen**. (II) is **nomegestrol** or its ester (specifically the acetate).

L121 ANSWER 3 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-308584 [32] WPIX
CR 2001-308582 [31]
DNC C2001-095360
TI Female **contraceptive** composition comprises **nomegestrol** (or ester) as progestational component and **estradiol** (or ester) as an **estrogenic** component in specific ratios for optimum menstrual cycle control.
DC B01
IN **PARIS, J; THOMAS, J**
PA (SOTH) **THERAMEX LAB SA**
CYC 92
PI WO 2001030358 A1 20010503 (200132)* FR 27p A61K031-57
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001010335 A 20010508 (200149) A61K031-57
ADT WO 2001030358 A1 WO 2000-FR2952 20001024; AU 2001010335 A AU 2001-10335

20001024
FDT AU 2001010335 A Based on WO 200130358
PRAI WO 1999-FR2587 19991025
IC ICM A61K031-57
ICS A61P005-30
AB WO 200130358 A UPAB: 20010831
NOVELTY - Female **contraceptive** compositions (A) comprises **nomegestrol** (or its ester) as progestational component (I) and **estradiol** (or its ester) as **estrogenic** component (II), associated or mixed with a diluent or vehicle, in a weight ratio of (I) to (II) at 0.5-5 (preferably 1-3).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the production of (A), by combining (I) and (II) with one or more of diluents, filler, compression adjuvants, lubricants and/or disintegrating agents.
ACTIVITY - Antifertility.
Tests in 18-35 year old women having normal menstrual cycles involving administration of **nomegestrol acetate** (Ia) and **estradiol** (IIa) showed that (IIa) at 1.5 mg daily (i.e. a dose insufficient to block **ovulation** if used alone) potentiated the anti-**ovulate** effect of (Ia), so that an adequate **ovulation** inhibiting effect was obtained at low doses of (Ia) (i.e. 0.625 mg per day).
MECHANISM OF ACTION - None given.
USE - (A) are used as **contraceptives**, specifically using a package containing 21-28 tablets of (A) and 0-7 placebo tablets (claimed).
ADVANTAGE - The (I)/(II) ratio is optimized to ensure good control of the menstrual cycle (claimed). The synthetic progestogen (I) are free of metabolic secondary effects. The antigonadotropic action of (I) is potentiated by (II), which also compensates for the **hypoestrogenia** induced by (II).
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B01-A02; B01-C02; **B14-P01B**

L121 ANSWER 4 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-308583 [32] WPIX
CR 2001-335679 [31]
DNC C2001-095359
TI Hormonal composition for treating menopausal **estrogen** deficiency, osteoporosis and cardiovascular disease, comprises combination of **estrogen** and progestogen derived from 19-norprogesterone.
DC B01
IN **PARIS, J; THOMAS, J**
PA (SOTH) **THERAMEX LAB SA**
CYC 92
PI WO 2001030357 A1 20010503 (200132)* FR 29p A61K031-57
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001010326 A 20010508 (200149) A61K031-57
ADT WO 2001030357 A1 WO 2000-FR2939 20001024; AU 2001010326 A AU 2001-10326 20001024
FDT AU 2001010326 A Based on WO 200130357
PRAI WO 1999-FR2588 19991025
IC ICM A61K031-57
ICS A61P005-30
AB WO 200130357 A UPAB: 20010831
NOVELTY - Hormonal compositions (A) comprise an orally administered **estrogen**-progestogen combination, allowing the simultaneous administration of an **estrogen** (I) at 0.3-3 mg and a progestogen (II) derived from 19-norprogesterone at 0.3-1.5 mg, (I) and (II) being associated or mixed with excipient(s).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the production of (A), by combining (I), (II) and excipient(s).

ACTIVITY - Osteopathic; cardiant; vasotropic.

In tests in menopausal women using 1.5 mg per day of **estradiol** in combination with various doses of **nomegestrol acetate** for 6 months, there was no significant difference in endometrial thickness between groups treated with 0.625, 1.25, 2.5 or 65 mg per day of **nomegestrol acetate**.

MECHANISM OF ACTION - None given.

USE - (A) is specifically used for treating **estrogen** deficiency, preventing osteoporosis and preventing cardiovascular diseases in menopausal women, by continuous or intermittent administration (all claimed). More generally (A) can be used for treating all types of **estrogen** deficiency in women.

ADVANTAGE - Functional disorders caused by menopausal **hypoestrogenia** are controlled while maintaining atrophy of the endometrium and preventing genital bleeding. The required therapeutic effects are obtained using markedly lower doses of (II) than those in related prior art compositions (see FR2754179), so that safety is improved.

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B01-A02; B01-C02; B14-D01B; B14-D01C; B14-F01; B14-N01
TECH UPTX: 20010611

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (I) is 17 beta-**estradiol** or its ester (specifically the valerate) or an equine conjugated **estrogen**. (II) is **nomegestrol** or its ester (specifically the acetate).

L121 ANSWER 5 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-308582 [32] WPIX
CR 2001-308584 [31]
DNC C2001-095358
TI A female **contraceptive** composition comprises **nomegestrol** (or ester) as progestational component and **estradiol** (or ester) as **estrogenic** component in specific ratios for optimum menstrual cycle control.
DC B01
IN **PARIS, J; THOMAS, J**
PA (PARI-I) PARIS J; (SOTH) **THERAMEX LAB SA**; (THOM-I) THOMAS J
CYC 18
PI WO 2001030355 A1 20010503 (200132)* FR 27p A61K031-57
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
ADT WO 2001030355 A1 WO 1999-FR2587 19991025
PRAI WO 1999-FR2587 19991025
IC ICM A61K031-57
ICS A61P005-30
AB WO 200130355 A UPAB: 20010611

NOVELTY - Female **contraceptive** compositions (A) comprise **nomegestrol** (or its ester) as progestational component (I) and **estradiol** (or its ester) as **estrogenic** component (II), associated or mixed with a diluent or vehicle, in a weight ratio of (I) to (II) at 0.5-5 (preferably 1-3).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the production of (A), by combining (I) and (II) with one or more of diluents, filler, compression adjuvants, lubricants and/or disintegrating agents.

ACTIVITY - Antifertility.

Tests in 18-35 year old women having normal menstrual cycles involving administration of **nomegestrol acetate** (Ia) and **estradiol** (IIa) showed that (IIa) at 1.5 mg daily (i.e. a dose insufficient to block **ovulation** if used alone) potentiated the anti-**ovulate** effect of (Ia), so that an adequate **ovulation** inhibiting effect was obtained at low doses of (Ia) (i.we. 0.625 mg per day).

MECHANISM OF ACTION - None given.

USE - (A) are used as **contraceptives**, specifically using a package containing 21-28 tablets of (A) and 0-7 placebo tablets (claimed).

ADVANTAGE - The (I)/(II) ratio is optimized to ensure good control of the menstrual cycle (claimed). The synthetic progestogen (I) are free of metabolic secondary effects. The antigonadotropic action of (I) is potentiated by (II), which also compensates for the **hypoestrogenia** induced by (II).

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B01-A02; B01-C02; **B14-P01B**

L121 ANSWER 6 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-040884 [05] WPIX
DNC C2001-011807
TI Method of **contraception** and for e.g. treating secondary amenorrhea, dysfunctional bleeding and endometriosis comprises administering progestational agent and bicyclic heterocyclic antiprogestin compound.
DC B01 B02
IN EDWARDS, J P; FENSOME, A; GRUBB, G S; JONES, T K; SANTILLI, A A; TEGLEY, C M; VIET, A Q; WROBEL, J E; ZHANG, P; ZHI, L; MARSCHKE, K B
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066225 A1 20001109 (200105)* EN 70p A61P015-18
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000051251 A 20001117 (200111) A61P015-18
EP 1173253 A1 20020123 (200214) EN A61P015-18
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000066225 A1 WO 2000-US11846 20000501; AU 2000051251 A AU 2000-51251 20000501; EP 1173253 A1 EP 2000-935851 20000501, WO 2000-US11846 20000501
FDT AU 2000051251 A Based on WO 200066225; EP 1173253 A1 Based on WO 200066225
PRAI US 2000-552545 20000419; US 1999-305007 19990504; US 1999-198246 19990504
IC ICM A61P015-18
ICS A61K031-565; A61K031-57; A61K045-06
ICI A61K031:565; A61K031:565; A61K031:54; A61K031:535; A61K031-57; A61K031-57
AB WO 200066225 A UPAB: 20010124
NOVELTY - Method of **contraception** comprises administration to a female for 28 consecutive days of:

(1) 14-24 daily doses of a progestational agent equal in activity to 35-100 mu g levonorgestrel;

(2) 1-11 daily doses of 2-50 mg bicyclic heterocyclic antiprogestin compound (I) and

(3) optionally a placebo for the remainder of 28 days.

DETAILED DESCRIPTION - Method of **contraception** comprises administration to a female for 28 consecutive days of:

(1) 14-24 (preferably 21) daily doses of a progestational agent equal in activity to 35-100 mu g levonorgestrel;

(2) 1-11 (preferably 3) daily doses of 2-50 mg bicyclic heterocyclic antiprogestin compound of formula (I) and

(3) optionally a placebo for the remainder (preferably 4) of the 28 days.

A, B = S, CH or N, provided that when A = S then B = CH or N, when B = S then A = CH or N and that both are not CH and when both are N then one is optionally substituted by 1-6C alkyl;

R1, R2 = H or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, aryl or heterocyclyl (all optionally substituted), CORA or NRBCORA or

R1 + R2 = 3-8C spiroalkyl, 3-8C spiroalkenyl or 3-8 membered

spiroheterocyclyl ring containing 1-3 O, S or N) heteroatoms;
RA = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
RB = H or optionally substituted 1-3C alkyl;
R3 = H, OH, NH2, optionally substituted 1-6C alkyl, optionally substituted 3-6C alkenyl, optionally substituted 3-6C alkynyl or CORC;
RC = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
R4 = phenyl substituted by X, Y and Z or 5- or 6-membered ring containing 1-3 O, S, SO, SO2 or NR5 heteroatoms and optionally substituted by 1 or 2 halo, CN, NO2, 1-3C alkyl, 1-3C alkoxy, 1-3C aminoalkyl, CORF or NRGCORF;
X = halo, CN, optionally substituted 1-3C alkyl, optionally substituted 1-3C alkoxy, optionally substituted 1-3C thioalkyl, optionally substituted 1-3C aminoalkyl, NO2, 1-3C perfluoroalkyl, 5-6 membered heterocyclyl containing 1-3 heteroatoms, CORD, OCORD or NRECORD;
RD = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
RE = H or optionally substituted 1-3C alkyl;
Y, Z = H, halo, CN, NO2, 1-3C alkoxy, 1-3C alkyl or 1-3C thioalkyl;
RF = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
RG = H or optionally substituted 1-3C alkyl;
R5 = H or 1-3C alkyl and
W = O or a bond

INDEPENDENT CLAIMS are included for the following:
(A) a method of **contraception** which comprises administration to a female of 18-21 daily doses of a progestational agent equivalent to 35-100 mu g levonorgestrel and 10-35 mu g ethinyl **estradiol**, 1-7 daily doses of 2-50 mg (I) and optionally a placebo for the remainder of the 28-day cycle;
(B) a method of **contraception** which comprises administration to a female of 18-21 daily doses of a progestational agent equivalent to 35-150 mu g levonorgestrel and 10-35 mu g ethinyl **estradiol**, 1-7 daily doses of 2-50 mg (I) and 10-35 mu g ethinyl **estradiol** and optionally a placebo for the remainder of the 28-day cycle and
(C) kits for the above methods.

ACTIVITY - Gynecological; cytostatic; anabolic.

USE - Useful for contraception and for treating secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon or prostate and minimizing the side effects of menstrual bleeding. The methods are also useful for stimulating food intake.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B01-A02; B01-C03; B01-C05; B01-C06; B01-C09; B06-H; B14-E11; B14-H01; B14-N14; B14-P02
TECH UPTX: 20010124

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred drugs: (I) Comprises 6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno(2,3-d)(1,3)oxazine-2-one (Ia).

The progestational agent is levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, **nomegestrol** or 17-deacetylnorgestimate.

L121 ANSWER 7 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-031720 [04] WPIX
DNC C2001-009622
TI Method of **contraception** and for treating e.g. secondary amenorrhea, dysfunctional bleeding and endometriosis by administering progestational agent and antiprogestin .
DC B02
IN EDWARDS, J P; FENSOME, A; GRUBB, G S; JONES, T K; PUWEN, Z; SANTILLI, A A;

TEGLEY, C M; TEREFENKO, E A; VIET, A Q; WROBEL, J E; ZHI, L
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066103 A2 20001109 (200104)* EN 61p A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000046749 A 20001117 (200111) A61K031-00
EP 1173208 A2 20020123 (200214) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000066103 A2 WO 2000-US11449 20000501; AU 2000046749 A AU 2000-46749 20000501; EP 1173208 A2 EP 2000-928519 20000501, WO 2000-US11449 20000501
FDT AU 2000046749 A Based on WO 200066103; EP 1173208 A2 Based on WO 200066103
PRAI US 2000-552037 20000419; US 1999-198238 19990504
IC ICM A61K031-00; A61K045-06
ICS A61K031-12; A61K031-495; A61K031-565; A61K031-57; A61P015-18
ICI A61K031-57, A61K031:495, A61K031:565; A61K031-57, A61K031:12, A61K031:565
AB WO 200066103 A UPAB: 20010118
NOVELTY - **Contraception** comprises administration to a female for 28 consecutive days:
(1) 14-21 daily doses of a progestational agent equivalent to 35-100 mu g levonorgestrel;
(2) 1 to 11 daily doses of 2-50 mg of an antiprogestin bicyclic heterocyclic compound (I) or its salts and
(3) optionally a placebo for the remainder of the 28-day cycle.
DETAILED DESCRIPTION - **Contraception** comprises administration to a female for 28 consecutive days:
(1) 14-21 daily doses of a progestational agent equivalent to 35-100 mu g levonorgestrel;
(2) 1 to 11 daily doses of 2-50 mg of an antiprogestin bicyclic heterocyclic compound of formula (I) or its salts and
(3) optionally a placebo for the remainder of the 28-day cycle.
A, B, D = N or CH, provided that not all are CH;
R1, R2 = H or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, aryl or heterocyclyl (all optionally substituted), CORA or NRBCORA or
R1 + R2 = 3-8C spiroalkyl, 3-8C spiroalkenyl or 3- to 8-membered spiroheterocyclyl ring containing 1-3 O, S or N heteroatoms (all optionally substituted by 1-4 F, 1-6C alkyl, 1-6C alkoxy, 1-6C thioalkyl, CF3, OH, CN, NH2, 1-6C alkylamino or di-(1-6C alkyl)-amino);
RA = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
RB = H or optionally substituted 1-3C alkyl;
R3 = H, OH, NH2, optionally substituted 1-6C alkyl, optionally substituted 3-6C alkenyl or CORC;
RC = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);
R4 = phenyl substituted by X, Y and Z or 5- or 6-membered ring containing 1-3 O, S, SO, SO2 or NR5 heteroatoms and optionally substituted by 1-2 halo, CN, NO2, 1-3C alkyl, 1-3C alkoxy, 1-3C aminoalkyl, CORF or NRGCORF;
X = halo, CN, optionally substituted 1-3C alkyl, optionally substituted 1-3C alkoxy, optionally substituted 1-3C thioalkoxy, NH2, optionally substituted 1-3C aminoalkyl, NO2, 1-3C perfluoroalkyl, 5- to 6-membered heterocyclyl (containing up to 3 heteroatoms), CORD, OCORD or NRECORD;
RD = H or 1-3C alkyl, aryl, alkoxy or 1-3C aminoalkyl (all optionally substituted);
RE = H or optionally substituted 1-3C alkyl;
Y, Z = H, halo, CN, NO2, 1-3C alkoxy, 1-3C alkyl or 1-3C thioalkoxy;
RF = H or 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted);

RG = H or optionally substituted 1-3C alkyl;
R5 = H or 1-3C alkyl;
Q = O, S, NR6 or CR7R8 and
W = O or a bond.
INDEPENDENT CLAIMS are included for the following:
(1) a method of **contraception** which comprises administering a first phase of 18-21 (preferably 21) daily dosage units of a progestational agent equivalent to 35-150 mu g levonorgestrel and ethinyl **estradiol** at a daily dosage of 10-35 mu g, a second phase of 1-7 (preferably 3) daily dosage units of (I) at a daily dosage of 2-50 mg and optionally a placebo for the remainder (preferably 4 daily dosage units) of a 28 day period;
(2) a method of **contraception** which comprises administering a first phase of 18-21 (preferably 21) daily dosage units of a progestational agent equivalent to 35-150 mu g levonorgestrel and ethinyl **estradiol** at a daily dosage of 10-35 mu g, a second phase of 1-7 (preferably 3) daily dosage units of (I) at a daily dosage of 2-50 mg and ethinyl **estradiol** at a concentration of 10-35 mu g and optionally a placebo for the remainder (preferably 4 daily dosage units) of a 28 day period and
(3) kits for daily oral administration as above.
ACTIVITY - Gynecological; cytostatic; anabolic.
USE - Useful for contraception and for treating secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon or prostate and minimizing the side effects of menstrual bleeding. The methods are also useful for stimulating food intake.
Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B01-A02; B01-C03; B01-C04; B01-C05; B01-C06; B01-C09; B06-A03; B06-E03; B06-H; B14-E11; B14-F02; B14-H01; B14-N14; **B14-P01** ; **B14-P01B**
TECH UPTX: 20010118
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred drugs: (I) Comprises 6-(3-chlorophenyl)-4,4-dimethyl-1,4-dihydro-3-oxa-1,8-diaza-naphthalene-2-one (Ia).
The progestational agent comprises levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, **nomegestrol** or 17-deacetylnorgestimate.

L121 ANSWER 8 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-024743 [03] WPIX
CR 2001-024742 [63]
DNC C2001-007495
TI **Contraceptive** compositions comprise quinazolinone and benzoxazine derivatives and is also useful for treatment/prevention of conditions such as amenorrhea, dysfunctional bleeding, uterine leiomyomata, carcinomas and endometriosis.
DC B01 B02
IN EDWARDS, J P; FENSOME, A; GRUBB, G S; JONES, T K; TEGLEY, C M; TEREFENKO, E A; WROBEL, J E; ZHANG, P; ZHI, L
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066165 A1 20001109 (200103)* EN 101p A61K045-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000045011 A 20001117 (200111) A61K045-06
EP 1173206 A1 20020123 (200214) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

ADT WO 2000066165 A1 WO 2000-US11644 20000501; AU 2000045011 A AU 2000-45011 20000501; EP 1173206 A1 EP 2000-926488 20000501, WO 2000-US11644 20000501
FDT AU 2000045011 A Based on WO 200066165; EP 1173206 A1 Based on WO 200066165
PRAI US 2000-552357 20000419; US 1999-183042 19990504
IC ICM A61K045-06
ICS A61K031-57; A61P015-18
ICI A61K031:565; A61K031:565; A61K031:565; A61K031:535; A61K031:495; A61K031:47; A61K031-57; A61K031-57; A61K031-57

AB WO 200066165 A UPAB: 20020301

NOVELTY - **Contraceptive** compositions comprise quinazolinone and benzoxazine derivatives and is also useful for treatment/prevention of conditions such as amenorrhea, dysfunctional bleeding, uterine leiomyomata, carcinomas and endometriosis.

DETAILED DESCRIPTION - A method of **contraception** comprises administering to a female of child bearing age for 28 consecutive days:

(a) a first phase of 14-24 daily dosage units of a progestational agent equal to 35-100 microgram levonorgestrel;

(b) a second phase of 1-11 daily dosage units, at a daily dosage of 2-50 mg of an antiproestin compound of formula (I) or its pharmaceutically acceptable salt

R1, R2 H, optionally substituted 1-6C alkyl, optionally substituted 2-6C alkenyl or alkynyl , optionally substituted 3-8C cycloalkyl, aryl, optionally substituted heterocyclic, CORA or NRBCORA; alternatively R1 and R2 are fused to form: (a) optionally substituted 3-8 membered spirocyclic alkyl ring; (b) optionally substituted 3-8 membered spirocyclic alkenyl; or (c) optionally substituted 3-8 membered heterocyclic ring containing 1-3 heteroatoms selected from O, S and N; the rings of (a), (b) and (c) are optionally substituted by 1-4 groups selected from F, 1-6C (alkyl, alkoxy or thioalkyl), CF3, OH, CN, NH2, -NH(1-6C alkyl) or -N(1-6Calkyl)2; RA is H, optionally substituted (1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl); RB is H or optionally substituted 1-3C alkyl; R3 = H, OH, NH2, optionally substituted(1-6C alkyl, 3-6C alkenyl or alkynyl) or CORC; RC = H, optionally substituted (1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl); R4 = H, halogen, CN, NO2, optionally substituted (1-6C alkyl, alkynyl, 1-6C alkoxy or 1-6C aminoalkyl) or amino; R5 = (a) or (b); (a) is trisubstituted benzene of formula (II) X = halogen, CN, optionally substituted (1-3C alkyl, alkynyl, 1-3C alkoxy, 1-3C thioalkoxy, 1-3C aminoalkyl), NO2, 1-3C perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms, CORD, OCORD or NRECORD; RD = H, optionally substituted (1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl); RE = H or optionally substituted 1-3C alkyl; Y, Z = H, halogen, CN, NO2, amino, aminoalkyl, 1-3C alkoxy, 1-3C alkyl or 1-3C thioalkoxy; (b) is 5 or 6 membered ring with 1,2, or 3 heteroatoms selected from O, S, SO2, or NR6 and containing 1 or 2 independent substituents selected from H, halogen, CN, NO2, amino, 1-3C alkyl, 1-3 C alkoxy, 1-3C aminoalkyl, CORF or NRGCORF; RF = H, optionally substituted(1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl); RG = H or optionally substituted 1-3C alkyl; R6 = H or 1-3C alkyl; G1 = O, NR7 or CR7R8; G2 = CO, CR7R8 provided that when G1 is O, G2 is CR7R8 and G1 and G2 cannot be both CR7R8; R7 and R8 = H or optionally substituted alkyl, aryl or heterocyclic moiety;

(c) optionally a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining 28 consecutive days in which no antiprogestin, progestin or **estrogen** is administered. The total daily dosage units of the first, second and third phase equals 28.

INDEPENDENT CLAIMS are is also included for:

(1) a method of **contraception** comprising administering to a female of child bearing age over a period of 28 consecutive days:

(a) a first phase of 18-21 daily dosage units of progestostational agent equal in progestational activity to 35-150 microgramme levonorgestrel and ethinyl **estradiol** art a daily dosage of 10-35 microgramme; and

(b) a second phase of 1-7 daily dosage units of an antiprogestin of above claim at a daily dose of 2-50 mg; and

(c) optionally an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days;

(2) a method of **contraception** comprising administering to a female of child bearing age over a period of 28 consecutive days:

(a) (a) a first phase of 18-21 daily dosage units of progestostational agent equal in progestational activity to 35-150 microgramme levonorgestrel and ethinyl **estradiol** at a daily dosage of 10-35 microgramme; and

(b) a second phase of 1-7 daily dosage units of an antiprogestin of above claim at a daily dose of 2-50 mg and ethinyl **estradiol** at a concentration of 10-35 microgramme; and

(c) optionally an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days, total daily dosage units being 28;

(3) a pharmaceutically useful kit adapted form daily oral administration comprising:

(1) a first phase of 14-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 microgramme of levonorgestrel;

(2) a second phase of 1-11 daily dosage units of an antiprogestin compound as above, each daily dosage unit comprising an antiprogestin compound at a daily dosage 2-50 mg; and

(3) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo. The total number of the daily dosage units in the three phases equals 28;

(4) a pharmaceutically useful kit adapted form daily oral administration comprising:

(a) a first phase of 18-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 microgramme of levonorgestrel and ethinyl **estradiol** at a daily dose of 10-35 microgramme;

(b) a second phase of 1-7 daily dosage units of an antiprogestin compound as above, each daily dosage unit comprising an antiprogestin compound at a daily dosage 2-50 mg; and

(c) a third phase of 0-9 daily dosage units of an orally and pharmaceutically acceptable placebo. The total number of the daily dosage units in the three phases equals 28; and

(5) a pharmaceutically useful kit adapted form daily oral administration comprising:

(a) a first phase of 18-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 microgramme of levonorgestrel and ethinyl **estradiol** at a daily dose of 10-35 microgramme;

(b) a second phase of 1-7 daily dosage units of an antiprogestin compound as above, each daily dosage unit comprising an antiprogestin compound at a daily dosage 2-50 mg and ethinyl **estradiol** at a concentration of 10-35 microgramme; and

(c) a third phase of 0-9 daily dosage units of an orally and pharmaceutically acceptable placebo. The total number of the daily dosage units in the three phases equals 28.

ACTIVITY - Gynecological; cytostatic.

MECHANISM OF ACTION - **contraceptive**; anticancer agent.

USE - The methods are useful for **contraception** or treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, polycyctic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate or minimization of side effects or cyclic menstrual bleeding. Additional uses include stimulation of food intake.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B01-A02; B06-D02; B06-D06; B14-H01; B14-N14; **B14-P01B**

TECH UPTX: 20010116

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The progestational agent is levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, methindrone acetate, norgestimate, osaterone, cycloproterone acetate, trimegestone, dienogest, dropsirenone, **nomegestrol** or (17-deacetyl)norgestimate

(especially levonorgestrel). The antiprogestin compound is selected from (9 compounds specified): 6-(3-chlorophenyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one or its pharmaceutically acceptable salt; 6(3-chlorophenyl)-4-cyclopropyl-1H-quinazolin-2-one or its pharmaceutically acceptable salt. Preparation - The antiprogestin compounds are prepared e.g. by treating appropriately substituted ortho-amino benzoic acid or derivative (1) with suitable organometallic agent, e.g. Grignard reagent, in appropriate non protic solvent to provide ortho-amino carbinol (2). Arylation of the aminocarbinol using Suzuki and Stille reaction conditions in the presence of transition metal catalysts with phosphino ligands or Pd-acetate with appropriately substituted nucleophilic agent such as aryl boronic acid, arylstannane etc to give compound (3). The compounds of the invention can be prepared from the carbinol 3 by reacting with appropriate ketone in the presence of suitable acid catalyst such as p-toluene sulfonic acid.

L121 ANSWER 9 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-024741 [03] WPIX
DNC C2001-007493
TI Method of **contraception** comprises administration of progestational agent, antiprogestin and optionally placebo over 28 day cycle.
DC B01 B02
IN COLLINS, M A; EDWARDS, J P; GRUBB, G S; JONES, T K; MACKNER, V A; TEGLEY, C M; WROBEL, J E; ZHI, L; MARSCHKE, K B
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066163 A1 20001109 (200103)* EN 43p A61K045-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000046819 A 20001117 (200111) A61K045-06
US 6319912 B1 20011120 (200174) A61K031-56
EP 1173209 A1 20020123 (200214) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000066163 A1 WO 2000-US11642 20000501; AU 2000046819 A AU 2000-46819 20000501; US 6319912 B1 Provisional US 1999-183023P 19990504, US 2000-552038 20000419; EP 1173209 A1 EP 2000-928610 20000501, WO 2000-US11642 20000501
FDT AU 2000046819 A Based on WO 200066163; EP 1173209 A1 Based on WO 200066163
PRAI US 2000-552038 20000419; US 1999-183023P 19990504
IC ICM A61K031-56; A61K045-06
ICS A61K031-535; A61K031-57; A61P015-18
ICI A61K031:565; A61K031:425; A61K031-57
AB WO 200066163 A UPAB: 20011203
NOVELTY - **Contraceptive** regimen comprising separate administration of progestational agent and antiprogestin over 28 day cycle.
DETAILED DESCRIPTION - A method of **contraception** comprises administering:
(a) a first phase of 14-24 daily dosage units of a progestational agent equal in progestational activity to 35-100 micro g levonorgestrel;
(b) a second phase of 1-11 daily dosage units, at a daily dosage of 2-50 mg of an antiprogestin compound of formula (I) or its salt; and
(c) optionally a third phase of daily disage units of an orally acceptable placebo for remaining days of the 28 consecutive days in which no antiprogestin, progestin or **estrogen** is administered;
to a female of child bearing age for 28 consecutive days. The total daily dosage units (a)-(c) equals 28.
R1, R2 = H, optionally substituted alkyl, OH, optionally substituted alkoxy, aryl or heteroaryl; arylalkyl, heteroarylalkyl or alkynyl; or
R1 + R2 = -CH2(CH2)nCH2-, -CH2CH2CMe2CH2CH2, -O(CH2)pCH2-,

O(CH2)qO-, -CH2CH2OCH2CH2-, -CH2CH2NR7CH2CH2-; or a double bond having two methyl groups, a cycloalkyl group, an oxygen bonded or a cycloether bonded to the terminal end;
R7 = H or 1-6C alkyl;
n = 1-5;
p,q = 1-4;
R3 = H, OH, NH2, CORa; optionally substituted alkyl; or alkenyl or alkynyl;
Ra = H; or optionally substituted alkyl, alkoxy or aminoalkyl;
R4 = H, halo, CN, NH2, optionally substituted alkyl, alkoxy, or optionally substituted aminoalkyl;
R5 = phenyl substituted by X, Y and Z;
X = halo, OH, CN; optionally substituted alkyl, alkoxy, thioalkyl or aminoalkyl; S(O)alkyl, S(O)2alkyl, NO2, perfluoroalkyl, 5 or 6 membered heterocycle containing 1-3 heteroatoms, thioalkoxy, -CORb, -OCORb or NRcCORb;
Rb = H; or optionally substituted alkyl, aryl, alkoxy or aminoalkyl;
Rc = H or optionally substituted alkyl;
Y, Z = H, halo, CN, NO2, alkoxy, alkyl or thioalkyl; or
R5 = 5 or 6 membered heteroaryl containing 1-3 O, S, SO, SO2 or NR6 and optionally substituted on C by 1-2 H, halo, CN, NO2, alkyl, alkoxy, aminoalkyl, CORd, or NReCORd;
Rd = H, or optionally substituted alkyl, aryl, alkoxy or aminoalkyl;
Re = H or optionally substituted alkyl;
R6 = H, alkyl, alkoxycarbonyl or is absent when the N or NR6 is bonded to a ring double bond.
INDEPENDENT CLAIMS are included for:
(1) a method of **contraception** comprising administering to a female of child bearing age over a period of 28 consecutive days:
(a) a first phase of 18-21 daily dosage units of progestational agent equal in progestational activity to 35-150 micro g levonorgestrel and ethinyl **estradiol** at a daily dosage of 10-35 micro g;
(b) a second phase of 1-7 daily dosage units of an antiprogestin as above at a daily dose of 2-50 mg and optionally 10-35 micro g ethinyl **estradiol**; and
(c) optionally an orally acceptable placebo for each remaining day of the 28 consecutive days;
(2) kits comprising the **contraceptive** regimens as above.
ACTIVITY - Contraceptive; gynecological; cytostatic. No relevant activity example given
MECHANISM OF ACTION - Progestational; antiprogestational.
USE - The methods are useful for contraception (claimed) and for hormone replacement therapy, in the treatment of endometriosis, luteal phase defects, benign breast and prostatic diseases and prostatic, ovarian, breast, uterine and endometrial cancers.
Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B01-C05; B06-F01; B14-D01C; B14-D02A; B14-H01; B14-N07A; B14-N14; **B14-P01B**
TECH UPTX: 20010116
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The progestational agent is levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cycloproterone acetate, trimegestone, dienogest, dropsirenone, **nomegestrol** or (17-deacetyl)norgestimate (especially levonorgestrel). The antiprogestin compound is 5-(3-chlorophenyl)-spiro(2,1-benzisothiazole-3(1H),1'-cyclohexane)2,2-dioxide or its pharmaceutically acceptable salt.

L121 ANSWER 10 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-007155 [01] WPIX
DNC C2001-001785
TI A method of **contraception** comprises administering substituted indoline derivatives useful also for e.g. the treatment and/or prevention of secondary amenorrhea and dysfunctional bleeding.

DC B01 B02
IN BENDER, R H W; EDWARDS, J P; GRUBB, G S; JONES, T K; MARSCHKE, K B; TEGLEY, C M; WROBEL, J E; ZHANG, P; ZHI, L
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066168 A1 20001109 (200101)* EN 86p A61K045-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000049801 A 20001117 (200111) A61K045-06
EP 1173213 A1 20020123 (200214) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000066168 A1 WO 2000-US11845 20000501; AU 2000049801 A AU 2000-49801 20000501; EP 1173213 A1 EP 2000-932006 20000501, WO 2000-US11845 20000501
FDT AU 2000049801 A Based on WO 200066168; EP 1173213 A1 Based on WO 200066168
PRAI US 2000-552355 20000419; US 1999-198249 19990504
IC ICM A61K045-06
ICS A61K031-57; A61P015-18
ICI A61K031:565; A61K031:565; A61K031:565; A61K031:565; A61K031:54; A61K031:535; A61K031:495; A61K031:41; A61K031-57; A61K031-57; A61K031-57; A61K031-57
AB WO 200066168 A UPAB: 20001230
NOVELTY - A method of **contraception** which comprises administering to a female of child bearing age substituted indoline derivatives (I) over 28 consecutive days.

DETAILED DESCRIPTION - A method of **contraception** which comprises administering to a female of child bearing age for 28 consecutive days: (a) a first phase of 14-24 daily dosage units of a progestational agent equal in progestational activity to 35-100 micro g levonorgestrel; (b) a second phase of 1-11 daily dosage units, at a daily dosage of 2-50 mg, of an antiprogestin compound of formula (I) or its salt; and optionally (c) a third phase of daily dosage units of a placebo for the remaining days of the 28 consecutive days in which no antiprogestin, progestin or **estrogen** is administered and the total daily dosage units of the first, second and third phases equals 28:

A = O, S or NR4;

B = bond between A and C=Q, or CR5R6;

R4, R5, R6 = H, optionally substituted 1-6C alkyl, optionally substituted 2-6C alkenyl, optionally substituted 2-6C alkynyl, optionally substituted 3-8C cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic or cyclic alkyl constructed by fusing R4 and R5 to form a 5-7 membered ring;

R1 = H, OH, NH2, optionally substituted 1-6C alkyl, 3-6C alkenyl, substituted 1-6C alkenyl, optionally substituted alkynyl or CORA;

RA = H, optionally substituted 1-3C alkyl, optionally substituted aryl, optionally substituted 1-3C alkoxy or optionally substituted 1-3C aminoalkyl;

R2 = H, halo, CN, NO2, optionally substituted 1-6C alkyl, optionally substituted 1-6C alkoxy or optionally substituted 1-6C aminoalkyl;

R3 = a or b;

a = benzene ring trisubstituted by X, Y or Z;

X = halo, CN, optionally substituted 1-3C alkyl, optionally substituted 1-3C alkoxy, optionally substituted 1-3C thioalkoxy, optionally substituted 1-3C aminoalkyl, NO2, 1-3C perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms, CORB, OCORB or NRCCORB;

RB = H, optionally substituted 1-3C alkyl, optionally substituted aryl, optionally substituted 1-3C alkoxy or optionally substituted 1-3C aminoalkyl;

RC = H or optionally substituted 1-3C alkyl;

Y, Z = H, halo, CN, NO2, 1-3C alkoxy, 1-3C alkyl or 1-3C thioalkoxy;

b = 5 or 6 membered ring with 1,2 or 3 heteroatoms from O, S, SO, SO2

or NR7 and containing 1 or 2 substituents from H, halo, CN, NO2, 1-3C alkyl, 1-3C alkoxy, 1-3C aminoalkyl, CORD or NRECORD;

RD = H, optionally substituted 1-3C alkyl, optionally substituted aryl, optionally substituted 1-3C alkoxy or optionally substituted 1-3C aminoalkyl;

RE = H or optionally substituted 1-3C alkyl; and

R7 = H or 1-3C alkyl.

INDEPENDENT CLAIMS are also included for the following:

(i) a method as above where the progestational agent is levonorgestrel and the antiprogestin is a compound of formula (II) or its salt;

(ii) a method of **contraception** which comprises administering to a female of child bearing age over a period of 28 consecutive days: (a) a first phase of 18-21 daily dosage units of progestational agent equal in progestational activity to 35-150 micro g levonorgestrel and ethinyl **estradiol** at a daily dose range of from 10-35 micro g; (b) a second phase of 1-7 daily dosage units of an antiprogestin (I) at a daily dose of 2-50 mg; and optionally (c) a placebo for each remaining day of the 28 consecutive days;

(iii) as in method (ii) except second phase is 1-7 daily dosage units, each daily dose unit containing an antiprogestin (I) at a concentration of 2-50 mg and ethinyl **estradiol** at a concentration of 10-35 micro g;

(iv) a kit adapted for oral administration over a 28 day period which comprises: (a) a first phase of 14-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 micro g levonorgestrel; (b) a second phase of 1-11 daily dosage units of an antiprogestin (I) at a daily dosage of 2-50 mg; and (c) a third phase of daily dosage units of a placebo;

(v) a kit adapted for oral administration over a 28 day period which comprises: (a) a first phase of 18-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 micro g levonorgestrel and ethinyl **estradiol** at a daily dose of 10-35 micro g; (b) a second phase of 1-7 daily dosage units of an antiprogestin (I) at a daily dosage of 2-50 mg; and (c) a third phase of daily dosage units of a placebo; and

(vi) a kit adapted for oral administration over a 28 day period which comprises: (a) a first phase of 18-21 daily dosage units of a progestational agent equal in progestational activity to 35-150 micro g levonorgestrel and ethinyl **estradiol** at a daily dose of 10-35 micro g; (b) a second phase of 1-7 daily dosage units of an antiprogestin (I) at a daily dosage of 2-50 mg and ethinyl **estradiol** at a concentration of 10-35 micro g; and (c) a third phase of from 0-9 daily dosage units of a placebo.

R1' = H, OH, NH2, optionally substituted 1-6C alkyl or CORA;

RA' = H, 1-4C alkyl or 1-4C alkoxy;

R2' = H, halo, CN, NO2 or optionally substituted 1-3C alkyl;

R3' = benzene disubstituted by X' at the 3' position and by Y' on 4' or 5' position;

X' = halo, CN, 1-3C alkoxy, 1-3C alkyl, NO2, 1-3C perfluoroalkyl, 5 membered heterocyclic ring containing 1-3 heteroatoms or 1-3C thioalkoxy; and

Y' = H, halo, CN, NO2, 1-3C alkoxy, 1-4C alkyl or 1-3C thioalkoxy.

ACTIVITY - Contraceptive; gynecological; cytostatic; anabolic.

MECHANISM OF ACTION - Progesterone receptor antagonists.

The compounds of the invention were tested in assays and their potency in the range of 0.01 nM to 5 mM in the vitro assays and 0.001-300 mg/kg in the in vivo assays. For one compound a IC50 (nM) hPR CV-1 of 147 was obtained.

USE - These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses include the stimulation of food intake.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B01-A02; B01-C04; B01-C05; B01-C06; B01-C09; B06-H; B14-D01B; B14-F08; B14-H01; B14-N14; **B14-P01B**
TECH UPTX: 20001230
TECHNOLOGY FOCUS - PHARMACEUTICALS - The progestational agent is selected from levonorgestrel, norgetrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, **nomegestrol** or (17-deacetyl)norgestimate.

L121 ANSWER 11 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-679728 [66] WPIX
DNC C2000-206816
TI **Contraception** method for cyclic combination therapy comprise indoline derivatives and progestational agents.
DC B01 B02
IN BENDER, R H W; EDWARDS, J P; FENSOME, A; GRUBB, G S; JONES, T K; MILLER, L L; TEGLEY, C M; ULLRICH, J W; WROBEL, J E; ZHANG, P; ZHI, L
PA (AMHP) AMERICAN HOME PROD CORP; (LIGA-N) LIGAND PHARM INC
CYC 93
PI WO 2000066167 A1 20001109 (200066)* EN 135p A61K045-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000048139 A 20001117 (200111) A61K045-06
EP 1173212 A1 20020123 (200214) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000066167 A1 WO 2000-US11834 20000501; AU 2000048139 A AU 2000-48139 20000501; EP 1173212 A1 EP 2000-930287 20000501, WO 2000-US11834 20000501
FDT AU 2000048139 A Based on WO 200066167; EP 1173212 A1 Based on WO 200066167
PRAI US 2000-552358 20000419; US 1999-183052 19990504
IC ICM A61K045-06
ICS A61K031-40; A61K031-565; A61P015-18
ICA A61K031-57
ICI A61K031:40, A61K031:565, A61K031:57; A61K031-40, A61K031:565
AB WO 200066167 A UPAB: 20001219
NOVELTY - Method of **contraception** comprises administering a first phase of 14-24 daily dosage units of a progestational agent, a second phase of 1-11 daily dosage units of an antiprogestin (I) over 28 days, and optionally a third phase comprising administering a placebo.
DETAILED DESCRIPTION - Method of **contraception** comprises administering to a woman of child bearing age for 28 consecutive days a first phase of 14-24 daily dosage units of a progestational agent equal in progestational activity to 35-100 micro g levonorgestrel, a second phase of 1-11 daily dosage units of 2-50 mg/day of an antiprogestin of formula (I) or its salts, and optionally a third phase comprising a placebo, where total daily dosage units of the phases equals 28.
R1, R2 = alkyl, alkoxy, aryl or heteroaryl (all optionally substituted), H, OH, OAc, arylalkyl, alkylheteroaryl, 1-propynyl or 3-propynyl; or
R1 + R2 = a ring comprising -CH2(CH2)nCH2-, -CH2CH2CMe2CH2CH2-, -O(CH2)mCH2-, -O(CH2)pO-, -CH2CH2OCH2CH2- or -CH2CH2N(H or alkyl)CH2CH2-; or
R1 + R2 = double bond to CMe2, C(cycloalkyl), O or C(cycloether);
n = 0-5;
m = 1-4;
p = 1-4;
R3 = 1-6C alkyl, 3-6C alkenyl or alkynyl (all optionally substituted), H, OH, NH2 or CORa;
Ra = 1-3C alkyl, 1-3C alkoxy, 1-3C or 1-3C aminoalkyl (all optionally substituted) or H;

R4 = 1-6C alkyl, 1-6C alkoxy or 1-6C aminoalkyl (all optionally substituted), H, NH2, CN or halo;

R5 = phenyl substituted by X, Y and Z, a 5-6 membered heterocycle with 1-3 NR6, O, S, SO2 or SO, and 1-2 W, or indol-4-yl, indol-7-yl or benzo-2-thiophene (optionally substituted with 1-3 halo, lower alkyl, CN, NO2, lower alkoxy or CF3);

X = 1-3C alkyl, 1-3C alkoxy, 1-3C thioalkyl or 1-3C aminoalkyl (all optionally substituted), halo, OH, CN, S(O)alkyl, S(O)2alkyl, NO2, a 5-6 membered heterocyclic ring containing 1-3 heteroatoms, CORb, OCORb or NRcCORb;

Y, Z = H, halo, CN, NO2, 1-3C alkyl, 1-3C alkoxy or 1-3C thioalkyl;

W = H, halo, CN, NO2, 1-3C alkyl, 1-3C alkoxy or 1-3C aminoalkyl, CORd or NReCORd;

R6 = H or 1-3C alkyl;

Rb, Rd = 1-3C alkyl, aryl, 1-3C alkoxy or 1-3C aminoalkyl (all optionally substituted) or H; and

Rc, Re = H or 1-3C alkyl (optionally substituted).

An INDEPENDENT CLAIM is included for a kit comprising 18-21 daily doses of levonorgestrel (35-100 micro g/day) and ethinyl **estradiol** (10-35 micro g/day), 1-7 daily doses of (I) (2-50 mg/day) and ethinyl **estradiol** (10-35 micro g/day) and daily placebos (up to 28 daily dosage units).

ACTIVITY - **Contraceptive**; gynecological; cytostatic; anabolic.

MECHANISM OF ACTION - Progesterone receptor antagonist.

In a rat decidudication assay, Ki (nM) and IC50 (nM) values against CV-1 cells for 5-(3-fluoro-5-nitrophenyl)spiro(cyclohexane-1,3-(3H)indol-2(1H)-one (I') were 9 and 1 respectively, with a decidual response of 60% at 10 mg/kg.

USE - As a method for **contraception** for females of child bearing age (claimed). The method may also be used for treatment of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis, polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon or prostate, minimization of side effects or cyclic menstrual bleeding, and for stimulation of food intake.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B01-A02; B01-C03; B01-C04; B01-C05; B01-C09; B06-B01; B06-D01; B12-M11; B14-D02A; B14-E11; B14-H01B; B14-N07A; B14-N14; **B14-P01B**
TECH UPTX: 20001219

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No suitable preparation given.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agent: The progestational agent is levonorgestrel (preferred), norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, cyproterone acetate, trimegestone, dienogest, drospirenone, **nomegestrol** or (17-acetyl)norgestimate.

L121 ANSWER 12 OF 12 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1997-145360 [13] WPIX
DNC C1997-046372
TI Oral treatment of **oestrogen** deficiency in menopausal women - by sequential admin. of dosage units contg. **oestrogen** only, **oestrogen** plus **progestagen** and placebo to re-establish the endometrial cycle.
DC B01
IN LANQUETIN, M; **PARIS, J**; **THOMAS, J L**; **THOMAS, J**
PA (SOTH) **THERAMEX LAB SA**
CYC 41
PI WO 9704784 A1 19970213 (199713)* FR 20p A61K031-57
RW: AT BE CH DE DK ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AU BR CA CN CZ FI HU IL JP KR MX NO RU SG US VN

```
     FR 2737411    A1 19970207 (199715)        16p    A61K031-57
     AU 9663674    A  19970226 (199725)               A61K031-57
     NO 9701449    A  19970530 (199732)               A61K000-00
     EP 783310     A1 19970716 (199733)  FR           A61K031-57
        R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
     ZA 9606545    A  19970730 (199735)        17p    A61K000-00
     BR 9606549    A  19980623 (199832)               A61K031-57
     JP 10507207   W  19980714 (199838)        17p    A61K031-565
     CZ 9700967    A3 19980812 (199839)               A61K031-57
     KR 97706004   A  19971103 (199844)               A61K031-57
     US 5891867    A  19990406 (199921)               A61K031-56
     HU 9900612    A2 19990728 (199936)               A61K031-57
     MX 9702381    A1 19980201 (199954)               A61K031-57
     AU 722355     B  20000727 (200041)               A61K031-57
     CN 1167438    A  19971210 (200165)               A61K031-57
ADT  WO 9704784 A1 WO 1996-IB754 19960729; FR 2737411 A1 FR 1995-9364 19950801;
     AU 9663674 A AU 1996-63674 19960729; NO 9701449 A WO 1996-IB754 19960729,
     NO 1997-1449 19970326; EP 783310 A1 EP 1996-923018 19960729, WO 1996-IB754
     19960729; ZA 9606545 A ZA 1996-6545 19960801; BR 9606549 A BR 1996-6549
     19960729, WO 1996-IB754 19960729; JP 10507207 W WO 1996-IB754 19960729, JP
     1997-507406 19960729; CZ 9700967 A3 WO 1996-IB754 19960729, CZ 1997-967
     19960729; KR 97706004 A WO 1996-IB754 19960729, KR 1997-702125 19970401;
     US 5891867 A WO 1996-IB754 19960729, US 1997-817329 19970424; HU 9900612
     A2 WO 1996-IB754 19960729, HU 1999-612 19960729; MX 9702381 A1 MX
     1997-2381 19970401; AU 722355 B AU 1996-63674 19960729; CN 1167438 A CN
     1996-191100 19960729
FDT  AU 9663674 A Based on WO 9704784; EP 783310 A1 Based on WO 9704784; BR
     9606549 A Based on WO 9704784; JP 10507207 W Based on WO 9704784; CZ
     9700967 A3 Based on WO 9704784; KR 97706004 A Based on WO 9704784; US
     5891867 A Based on WO 9704784; HU 9900612 A2 Based on WO 9704784; AU
     722355 B Previous Publ. AU 9663674, Based on WO 9704784
PRAI FR 1995-9364     19950801
REP  2.Jnl.Ref; DE 3229612; WO 9406437
IC   ICM  A61K000-00; A61K031-56; A61K031-565; A61K031-57
     ICS  A61K009-20
ICI  A61K031-57, A61K031:565; A61K031-57, A61K031:565; A61K031-57, A61K031:565
AB   WO   9704784 A UPAB: 19970326
       Oestrogen deficiency in menopausal women is treated by oral
     admin., during the whole of the month, of, in sequence, (a)
     oestrogen (I) only; (b) (I) plus a progestagen (II) and
     (c) a placebo.
          USE - The treatment is used to compensate functional disorders
     characteristic of (post)menopausal hypo-oestrogenism, esp. to
     re-establish the endometrial cycle and to reduce the number of hot
     flushes. The treatment also slows down post-menopausal bone restructuring,
     so may prevent osteoporosis.
     Dwg.0/0
FS   CPI
FA   AB; DCN
MC   CPI: B04-J02; B14-N14


=> d his

     (FILE 'HOME' ENTERED AT 13:42:22 ON 15 MAR 2002)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 13:42:43 ON 15 MAR 2002
L1             1 S NOMEGESTROL/CN
L2             1 S NOMEGESTROL ACETATE/CN
L3             1 S ESTRADIOL/CN

     FILE 'EMBASE' ENTERED AT 13:43:28 ON 15 MAR 2002
L4           263 S L1 OR L2
L5           267 S NOMEGESTROL OR NOMEGESTROL ACETATE
L6           151 S TX071 OR TX066 OR TX()(071 OR 066) OR LUTENYL OR UNIPLANT
```

```
L7          267 S L4-L6
L8        42996 S L3
L9        60794 S ESTRADIOL
L10       60794 S L8,L9
L11       67578 S GESTAGEN+NT/CT
                E PROGESTAGEN/CT
                E E3+ALL
L12       67579 S L7,L11
L13       93648 S ESTROGEN+NT/CT
                E SYNTHETIC/CT
L14      102037 S L10,L13
L15       38896 S L12 AND L14
L16      216929 S DRUG COMBINATION+NT/CT
L17        6314 S L15 AND L16
L18          37 S L5/CT (L) CB/CT
L19        1774 S L9/CT (L) CB/CT
L20          24 S L18 AND L19
L21          24 S L20 AND L15,L17
L22       51142 S CONTRACEPTION+NT/CT
L23        8046 S L22 AND L15
L24           5 S L23 AND L21
L25           2 S L24 AND CONTRACEPT?/TI,BI,CT
L26        1517 S L17 AND L23
L27         182 S L23 AND L18,L19
L28        1517 S L26,L27
                E CONTRACEPTION/CT
                E E3+ALL
L29       21785 S E4 OR E12 OR E30 OR E31 OR E32 OR E33 OR E34 OR E35 OR E36 OR
L30        1122 S L29  AND L28
L31          13 S L30 AND L7
L32         346 S L30 AND L10
L33           7 S L32 AND L31
L34          71 S L29 AND L7
L35          19 S L34 AND L10
L36          16 S L35 AND PY<=1999
                SEL DN 9 12
L37           2 S L36 AND E1-E2
L38           2 S L25,L37
                E OVULATION/CT
                E E3+ALL
L39        8341 S E1
                E OVULATION/CT
                E E6+AKK
                E E3+ALL
L40         870 S E2+NT
L41        1673 S L39,L40 AND L15
L42          11 S L41 AND L7
L43          99 S L7 AND L9/CT
L44          10 S L43 AND L29
L45           5 S L43 AND L39,L40
L46          12 S L44,L45
                E ESTRADIOL/CT
                E ESTRADIOL PLUS/CT
L47          68 S ESTRADIOL PLUS?/CT AND L17-L21
L48        1596 S L17-L21 AND PLUS NOT L47
L49          16 S L48 AND L7
L50           2 S L38 AND L4-L49

     FILE 'EMBASE' ENTERED AT 14:15:38 ON 15 MAR 2002
L51        6263 S L11 (L) CB/CT
L52          70 S L7 AND L51
L53          32 S L52 AND L19
L54           2 S L53 AND (CONTRACEP? OR OVULAT? OR BIRTH(L)CONTROL? OR PREGNAN
L55           0 S L54 NOT L50

     FILE 'MEDLINE' ENTERED AT 14:17:43 ON 15 MAR 2002
```

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L56          98 S L7
L57       66096 S L10
L58          45 S L56 AND L57
                SEL DN AN 16 38  39
L59           3 S L58 AND E1-E9
L60          11 S L58 AND CONTRACEP?
L61           3 S L60 AND L59
L62           8 S L60 NOT L61
                E CONTRACEPT/CT
L63           0 S E4+NT AND L58
L64          42 S E44+NT AND L58
L65          42 S E46+NT AND L58
L66           0 S E124+NT AND L58
L67           0 S E125+NT AND L58
L68          42 S E198+NT AND L58
L69           4 S E199+NT AND L58
L70          38 S E222+NT AND L58
L71           2 S E246+NT AND L58
L72          15 S E259+NT AND L58
L73           1 S E310+NT AND L58
L74           1 S E326+NT AND L58
L75          42 S L64-L74
L76          19 S L75 AND COMBIN?
L77          16 S L75 AND (COADMINT? OR COMED? OR COPRESCRI? OR COTHERAP? OR PL
L78          24 S L76,L77
L79           9 S L78 NOT ?MENOPAUS?
                SEL DN 2 4 6 7 8 AN
L80           5 S L79 AND E1-E15
L81           5 S L61,L80 AND L56-L80
L82           1 S L58 AND COADMIN?
L83           5 S L81,L82

     FILE 'MEDLINE' ENTERED AT 14:33:39 ON 15 MAR 2002

     FILE 'WPIX' ENTERED AT 14:33:54 ON 15 MAR 2002
L84          15 S  L5,L6
L85         563 S ?GESTAGEN?
L86        5048 S ?ESTRADIOL? OR ?ESTROG?
                E NOMEGESTROL/DCN
                E  ESTRADIOL/DCN
                E E3+ALL
L87         877 S E2 OR 0014/DRN
L88           4 S E4
L89          70 S E6 OR 0024/DRN
L90          15 S E8
L91           8 S E10
L92          80 S E12
L93          60 S E16
L94           3 S E18
L95           2 S E20
L96         194 S E24 OR 0013/DRN
L97           6 S E26
L98           2 S E28
L99         216 S E32 OR 0069/DRN
L100          4 S E34
L101         23 S E36
L102         26 S E38
L103          1 S E40
L104        259 S L84,L85 AND L86-L103
L105         52 S L104 AND (P841 OR P841 OR P843 OR P840)/M0,M1,M2,M3,M4,M5,M6
L106        111 S (B12-K03 OR C12-K03 OR B14-P01 OR C14-P01 OR B14-P01B OR C14-
L107         13 S L104,L106 AND L84
                E PARIS J/AU
L108         95 S E3-E10
                E THOMAS J/AU
L109        220 S E3,E17,E18
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L110          5 S L108,L109 AND L104
                E THERAMEX/PA
L111          5 S E3,E4,E5 AND L104
L112          5 S L110,L111
L113          4 S L107 AND L112
L114          5 S L112,L113
L115          9 S L107 NOT L114
L116          7 S L115 NOT (DEHYDROGENASE OR TESTOSTERONE)/TI
L117          9 S L114,L116 AND ?CONTRACEP?
L118          2 S L114,L116 AND OVUL?
L119          9 S L117,L118
L120          3 S L114,L116 NOT L119
L121         12 S L119,L120 AND L84-L120

     FILE 'WPIX' ENTERED AT 14:42:35 ON 15 MAR 2002
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

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=> d his

     (FILE 'HOME' ENTERED AT 11:04:48 ON 15 MAR 2002)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 11:05:07 ON 15 MAR 2002
               E NOMEGESTROL/CN
L1             1 S E3
L2             1 S E4
L3             2 S L1,L2
               SEL RN
L4             0 S E1-E2/CRN
               E ESTRADIOL/CN
L5             1 S E3
               SEL RN
L6           135 S E1/CRN

     FILE 'HCAPLUS' ENTERED AT 11:06:59 ON 15 MAR 2002
L7            79 S L3
L8            85 S NOMEGESTROL OR NOMEGESTROL ACETATE OR TX071 OR TX066 OR TX()(
L9            94 S L7,L8
L10          730 S GESTAGEN
L11           10 S NORPREGNA(L)DIENE(L)DIONE(L)METHYL(L)(HYDROXY OR ACETYLOXY)(L
L12           12 S NORPREGNA(L)DIENE(L)DIONE(L)METHYL(L)(HYDROXY OR ACETOXY)(L)1
L13           12 S L11,L12
L14            1 S L13 AND L9
L15           94 S L9,L14
L16          886 S GESTAGEN?
L17          886 S L10,L16
L18        43509 S L5
L19          642 S L6
L20        62702 S ESTRADIOL
L21        72884 S ?ESTROGEN?
               E ESTROGEN/CT
               E E33+ALL
L22        33184 S E7,E6+NT
L23           37 S L15 AND L18,L19,L20
L24          484 S L15,L17 AND L18-L22
L25            8 S CONTRACEPT? AND L23
L26          164 S CONTRACEPT? AND L24
L27          164 S L25,L26
L28           92 S L23,L24 AND (OVULAT? OR OVARY)
L29           78 S L23,L24 AND OVARIAN
               E CONTRACEPT/CT
               E E7+ALL
L30          117 S E4+NT AND L23,L24
L31            5 S E8+NT AND L23,L24
               E E8+ALL
L32           73 S E2+NT AND L23,L24
L33           21 S (FERTIL? OR INFERTIL?) AND L23,L24
L34          256 S L27-L33
               E ORAL CONTRACEPTIVE/CT
               E E4+ALL
L35           59 S E1,E2 AND L23,L24
               E OVAR/CT
               E E15+ALL
L36           56 S E3+NT AND L23,L24
L37            4 S E16+NT AND L23,L24
L38            0 S E18+NT AND L23,L24
L39            1 S E21+NT AND L23,L24
               E OVAR/CT
               E E29+ALL
L40            5 S E1,E2 AND L23,L24
L41          259 S L34-L40
L42          456 S L23,L24 AND (PD<=19991025 OR PRD<=19991025 OR AD<=19991025)
               E PARIS J/AU
```

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L43          17 S E3-E16 AND L23,L24
                E THOMAS J/AU
L44           1 S E3,E4,E38,E39 AND L23,L24
                E THOMAS JEAN/AU
L45           7 S E3,E12,E14 AND L23,L24
L46          18 S L43-L45 AND L42
L47           3 S L41 AND L46
                E THERAMEX/PA,CS
L48          13 S L23,L24 AND E3-E8
L49          12 S L48 AND L42
L50           3 S L49 AND L41
L51           4 S L47,L50
L52           2 S L51 AND (COMPOSITION OR MEDICINE)/TI
L53          15 S L46,L49 NOT L51-L52
                SEL DN 1 2 4 5 6 14
L54           6 S L53 AND E1-E6
L55           8 S L52,L54
L56         272 S L23,L24 AND (COADMIN? OR COMEDIC? OR COPRESCRI? OR COTHERAP?
L57          24 S L56 AND COMPOSITION/CW
L58         248 S L56 NOT L57
L59          24 S L58 AND L9
L60          19 S L59 AND L18,L20
L61           5 S L59 NOT L60
                SEL DN 2 3
L62           2 S L61 AND E7-E8
L63          10 S L55,L62
L64          13 S L60 NOT L63
L65           7 S L63,L64 AND ?CONTRACEPT?
L66         164 S L23,L24 AND ?CONTRACEPT?
L67          10 S L66 AND L9
L68           9 S L67 NOT CRYST?/TI
L69          10 S L65,L68
L70          16 S L63,L64 NOT L69
L71           9 S L70 AND (PARIS ? OR THOMAS ?)/AU
L72           5 S L70 AND THERAMEX/PA,CS
L73          19 S L69,L71,L72
L74          15 S L73 NOT (CRYST? OR ULTRASOUND OR UREA OR OXOSPIRO)/TI
L75           4 S L73 NOT L74

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:55:09 ON 15 MAR 2002
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FILE COVERS 1907 - 15 Mar 2002  VOL 136 ISS 11
FILE LAST UPDATED: 13 Mar 2002  (20020313/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.
```

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

=> d l74 all tot

L74 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:903818 HCAPLUS
DN 136:15686
TI Starter kit for low dose oral **estrogen contraceptives**
IN Grubb, Gary S.
PA American Home Products Corporation, USA
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 2-3 (Mammalian Hormones)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001093848	A2	20011213	WO 2001-US18142	20010605
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002010167	A1	20020124	US 2001-872250	20010601
PRAI	US 2000-210310	P	20000608		

AB An oral **contraceptive** starter kit comprising at least two cycle packs of **compns**. contg. an **estrogen** and a progestin is described. The **contraceptive** kit helps to overcome or ameliorate the problem of breakthrough bleeding and spotting assocd. with lowest dose (15-20 .mu.g ethynyl **estradiol**) **estrogen contraceptives**. For example, a kit with three cycle packs contained: (cycle 1) levonorgestrel (LNG) 150 .mu.g and ethynyl **estradiol** (EE) 30 .mu.g (21 days), (cycle 2) LNG 50 .mu.g and EE 30 .mu.g (6 days), LNG 75 .mu.g and EE 40 .mu.g (5 days), and LNG 125 .mu.g and EE 30 .mu.g (10 days), and (cycle 3) LNG 100 .mu.g and EE 20 .mu.g (21 days).
ST **estrogen** progestin oral **contraceptive** kit
IT Drug delivery systems
(oral; starter kit for low dose oral **estrogen contraceptives**)
IT **Estrogens**
Progestogens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(starter kit for low dose oral **estrogen contraceptives**)
IT 51-98-9, Norethindrone acetate 52-76-6, Lynestrenol 57-63-6, Ethynyl **estradiol** 68-22-4, Norethindrone 68-23-5, Norethynodrel 71-58-9, Medroxyprogesterone acetate 297-76-7, Ethynodiol diacetate 427-51-0, Cyproterone acetate 595-33-5, Megestrol acetate 797-63-7, Levonorgestrel 6533-00-2, Norgestrel 35189-28-7, Norgestimate 53016-31-2, 17-Deacetylnorgestimate 54024-22-5, Desogestrel 54048-10-1, 3-Ketodesogestrel **58691-88-6, Nomegestrol** 60282-87-3, Gestodene 67392-87-4, Drospirenone 74513-62-5,

Trimegestone 105149-04-0, Osaterone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(starter kit for low dose oral **estrogen contraceptives**)

L74 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:319731 HCAPLUS
DN **134:316160**
TI Hormonal composition based on a progestational agent and an **estrogen**
IN **Paris, Jacques; Thomas, Jean-louis**
PA Laboratoire **Theramex**, Monaco
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM A61K031-57
ICS A61P005-30
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001030356	A1	20010503	WO 1999-FR2588	19991025 <--
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
WO 2001030357	A1	20010503	WO 2000-FR2939	20001024 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI WO 1999-FR2588 W 19991025 <--

AB The invention concerns the field of therapeutic chem. and more particularly the field of hormonal pharmaceutics technique. More precisely, it concerns novel hormonal compns. formed by an progestogen-**estrogen** combination consisting of an **estrogen** compd. and a progestational compd., assocd. or mixed with one or several pharmaceutically acceptable inert non-toxic carriers designed for oral administration. The invention also concerns the use of the progestogen-**estrogen** mixt. wherein the **estrogen** constituent and the progestogen constituent are administered in combination. The combined assocn. can be prescribed continuously or intermittently, so as to produce a compn. for treating **estrogen** deficiencies, preventing osteoporosis and cardiovascular diseases in postmenopausal women. The invention further concerns a method for prepg. said novel pharmaceutical progestogen-**estrogen** compns. A tablet contained **estradiol** 0.811, **nomegestrol acetate** 0.338, lactose 71.238, cellulose 15.032, povidone 7.297, Precirol AT05 1.503, colloidal silica 0.540, and crospovidone 3.243%. Antimitotic effects of the compn. in endometrial cells was studied.

ST hormone progestational agent **estrogen**; tablet **estradiol nomegestrol acetate** antimitotic

IT **Estrogens**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugated; hormonal compn. based on progestational agent and **estrogen**)

IT Cardiovascular system
(disease; hormonal compn. based on progestational agent and **estrogen**)

IT Menopause
(hormonal compn. based on progestational agent and **estrogen**)
IT **Estrogens**
Hormones, animal, biological studies
Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hormonal compn. based on progestational agent and **estrogen**)
IT Mitosis
(inhibitors; hormonal compn. based on progestational agent and **estrogen**)
IT Drug delivery systems
(tablets; hormonal compn. based on progestational agent and **estrogen**)
IT Osteoporosis
(therapeutic agents; hormonal compn. based on progestational agent and **estrogen**)
IT Drug delivery systems
(unit doses; hormonal compn. based on progestational agent and **estrogen**)
IT **50-28-2, Estradiol**, biological studies 472-54-8, 19-Norprogesterone 979-32-8, **Estradiol** valerate **58652-20-3, Nomegestrol acetate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hormonal compn. based on progestational agent and **estrogen**)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Boissonneault, R; US 5208225 A 1993 HCAPLUS
(2) Laboratoire Theramex; FR 2754179 A 1998 HCAPLUS
(3) Plunkett, E; EP 0136011 A 1985 HCAPLUS

L74 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:319730 HCAPLUS
DN 134:316159
TI **Contraceptive medicine** based on a progestational agent and an **estrogen**
IN **Paris, Jacques; Thomas, Jean-louis**
PA Laboratoire **Theramex**, Monaco
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM A61K031-57
ICS A61P005-30
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001030355	A1	20010503	WO 1999-FR2587	19991025 <--
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
WO 2001030358	A1	20010503	WO 2000-FR2952	20001024 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRAI WO 1999-FR2587	W	19991025 <--		

AB The invention concerns the field of chem. and more particularly the field of therapeutic chem. More particularly, it concerns novel **contraceptive** compns. consisting of a progestational agent and an **estrogen**. It specifically concerns novel pharmaceutical **contraceptive** compns. characterized in that they contain as active principles a **nomegestrol** and **estradiol** ester combined or mixed with a pharmaceutically acceptable inert non-toxic carrier or support suited for oral administration. A tablet contained 2.5% **estradiol** premixt. 44.45, **nomegestrol acetate** 0.33, colloidal silica 0.55, Crospovidone 3.60, lactose 28.89, microcryst. cellulose 19.18, stearic acid 2.00, and talc 1.00%. Antigonadotropic efficacy of the combination was studied in female volunteers.

ST oral **contraceptive** progestational agent **estrogen**; **estradiol nomegestrol acetate** tablet oral **contraceptive**

IT Drug delivery systems
(capsules; **contraceptive** medicine based on progestational agent and **estrogen**)

IT Lubricants
(**contraceptive** medicine based on progestational agent and **estrogen**)

IT **Estrogens**
Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**contraceptive** medicine based on progestational agent and **estrogen**)

IT **Contraceptives**
(**oral**; **contraceptive** medicine based on progestational agent and **estrogen**)

IT Drug delivery systems
(powders; **contraceptive** medicine based on progestational agent and **estrogen**)

IT Drug delivery systems
(sachets; **contraceptive** medicine based on progestational agent and **estrogen**)

IT Drug delivery systems
(tablets; **contraceptive** medicine based on progestational agent and **estrogen**)

IT **50-28-2D, Estradiol**, ethers and esters
58652-20-3, Nomegestrol acetate
58691-88-6D, Nomegestrol, ethers and esters
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**contraceptive** medicine based on progestational agent and **estrogen**)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Laboratoire Theramex; FR 2754179 A 1998 HCAPLUS

L74 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:854101 HCAPLUS

DN 134:37255

TI **Nomegestrol acetate** and vascular reactivity: nonhuman primate experiments

AU **Paris, J. M.**; Williams, K. J.; Hermsmeyer, K. R.; Delansorne, R.

CS BP 59, Laboratoire **Theramex**, 98007, Monaco

SO Steroids (2000), 65(10-11), 621-627
CODEN: STEDAM; ISSN: 0039-128X

PB Elsevier Science Inc.

DT Journal

LA English

CC 2-4 (Mammalian Hormones)

AB Prevention of coronary artery disease has been recognized as a major

benefit of **estrogen** replacement therapy (ERT) in postmenopausal women. However, endometrial hyperplasia induced by unopposed ERT has raised important safety concerns. Progesterone or synthetic progestins have been used in **combined** hormone replacement therapy (HRT) to prevent endometrial cancer risk. Therefore, a major concern has been to ensure that the vascular beneficial effects of **estrogens** are not opposed when **combined** with progestins. **Nomegestrol acetate** (NOMAC) is an orally active progestin widely prescribed for HRT. Its vascular effects were evaluated in two models of coronary vascular reactivity in primates: the paradoxical vasoconstriction to acetylcholine (Ach) coronary infusion after 5 mo of mildly atherogenic diet in ovariectomized (OVX) Cynomolgus monkeys and the pharmacol. evoked coronary vasospasm in the OVX Rhesus monkey. In the first model, after 3 mo of continuous oral administration in the diet at 0.1 mg/kg/day, E2 prevented the paradoxical response to Ach, alone as well as **combined** with 0.25 mg/kg/day NOMAC, whereas NOMAC counteracted the endometrial stimulation. In the second model, after one artificial cycle consisting of 28 days of E2 s.c. implant and of daily oral gavage with 1 mg/kg/day of NOMAC for the last 14 days, no vasospasm (0 of 11 tested animals) occurred when the complete challenge protocol, including serotonin and the thromboxane agonist U46619, was administered to OVX Rhesus monkeys. In the balanced crossover design, identical artificial cycles with medroxyprogesterone acetate (MPA) at the same dose resulted in 7 vasospasms in 12 animals. In parallel, effective progestative activity was demonstrated by a secretory pattern in endometrial sections obtained at the end of the cycle. In these two nonhuman primate cardiovascular models, NOMAC did not have the negating effects obsd. with MPA.

ST **nomegestrol acetate estradiol** HRT
postmenopause blood vessel endometrium monkey

IT Artery, disease
(coronary, spasm; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Artery, disease
(coronary; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Uterus, disease
(endometrium, hyperplasia; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Uterus
(endometrium; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Lipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(high-d., cholesterol ester-contg.; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Blood plasma
Hormone replacement therapy
Vasoconstriction
(**nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT **Estrogen** receptors
Glycerides, biological studies
Progesterone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT Menopause

(postmenopause; **nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT **50-28-2, Estradiol**, biological studies 71-58-9, Medroxyprogesterone acetate **58652-20-3, Nomegestrol acetate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

IT 57-88-5, Cholesterol, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nomegestrol acetate** and vascular reactivity in nonhuman primates in relation to role of progestins in hormone replacement therapy)

RE.CNT 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L74 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:790346 HCAPLUS
DN **133:330062**
TI **Contraceptive compositions** containing 2,1-benzisothiazoline 2,2-dioxides and progestationals
IN Grubb, Gary S.; Zhi, Lin; Jones, Todd K.; Marschke, Keith B.; Tegley, Christopher M.
PA American Home Products Corporation, USA; Ligand Pharmaceuticals, Inc.
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06

ICS A61K031-57; A61P015-18; A61K031-57; A61K031-425; A61K031-565
CC 2-3 (Mammalian Hormones)
Section cross-reference(s): 28, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000066163	A1	20001109	WO 2000-US11642	20000501
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6319912	B1	20011120	US 2000-552038	20000419
EP 1173209	A1	20020123	EP 2000-928610	20000501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1999-183023 P 19990504
US 2000-552038 A1 20000419
WO 2000-US11642 W 20000501
OS MARPAT 133:330062
AB This invention relates to cyclic **combination** therapies utilizing, in **combination** with a progestin, an **estrogen**, or both, and progesterone receptor antagonists 2,1-benzisothiazoline 2,2-dioxides. 5-(3-Chlorophenyl)spiro[2,1-benzisothiazole-3(1H),1'-cyclohexane] 2,2-dioxide was prepd. and the antiprogestational activity of this compd. was demonstrated in a conventional pharmacol. test.
ST **contraceptive** progestagen benzisothiazoline dioxide
IT Progestogens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprogestins; **contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
IT **Contraceptives**
(**contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
IT 304681-96-7P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
IT 628-77-3, 1,5-Diiodopentane 76513-69-4, 2-(Trimethylsilyl)ethoxymethyl chloride 111248-89-6
RL: RCT (Reactant)
(**contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
IT 304681-97-8P 304681-98-9P 304681-99-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(**contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
IT 51-98-9, Norethindrone acetate 68-22-4, Norethindrone 427-51-0, Cyproterone acetate 797-63-7, Levonorgestrel 6533-00-2, Norgestrel 35189-28-7, Norgestimate 53016-31-2, 17-Deacetylnorgestimate 54024-22-5, Desogestrel 54048-10-1, 3-Ketodesogestrel **58691-88-6**, **Nomegestrol** 60282-87-3, Gestodene 65928-58-7, Dienogest 67392-87-4, Drospirenone 74513-62-5, Trimegestone 105149-04-0, Osaterone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**contraceptive compns**. contg. 2,1-benzisothiazoline 2,2-dioxides and progestationals)
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(3) Butti, A; US 4093730 A 1978
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L74 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:193986 HCAPLUS
DN 130:213664
TI Hormonal **contraceptive**
IN Hesch, Rolf-Dieter
PA Germany
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9912531	A2	19990318	WO 1998-DE2636	19980903
	WO 9912531	A3	19990923		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	DE 19739916	A1	19990318	DE 1997-19739916	19970911
	DE 19739916	C2	20010913		
	AU 9911409	A1	19990329	AU 1999-11409	19980903
	EP 1011682	A2	20000628	EP 1998-954135	19980903
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	DE 1997-19739916	A	19970911		
	WO 1998-DE2636	W	19980903		

AB A hormonal **contraceptive** comprises a 1st hormonal component contg. .gtoreq.1 **gestagen** or antigestagen and a 2nd hormonal component contg. .gtoreq.1 **estrogen** or **antiestrogen**, for continuous and **combined** administration. This **compn** . inhibits ovulation and guarantees high **contraceptive** efficiency and reliable suppression of the menstrual cycle at very low doses, and can be used to treat mammary tumors. Continuous administration of **estrogen** favorably affects premenstrual syndrome and does not alter the equil. in the blood coagulation system, thereby avoiding the risk of thrombosis. The hormones may be administered orally, transdermally, intravaginally, or as sustained-release injections or implants. Thus, daily consumption of a tablet contg. 5 .mu.g ethynylestradiol and 2 mg norethisterone acetate by women for 9 mo provided good **contraception** and complete suppression of menstruation with practically no side effects.

ST **contraceptive** female **estrogen gestagen**

IT Breast tumor inhibitors
Contraceptives
Implants (drug delivery systems)
Oral **contraceptives**
Oral drug delivery systems
Transdermal drug delivery systems
Vaginal drug delivery systems
(hormonal **contraceptive**)

IT **Antiestrogens**
Antiprogestins

Estrogens
Progestins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hormonal **contraceptive**)
IT Sustained release drug delivery systems
(injections; hormonal **contraceptive**)
IT Injections (drug delivery systems)
(sustained release; hormonal **contraceptive**)
IT 50-27-1, Estriol **50-28-2**, 17.beta.-**Estradiol**, biological studies 51-98-9, Norethisterone acetate 52-76-6, Lynestrenol 53-16-7, Estrone, biological studies 57-63-6, Ethynylestradiol 57-83-0, Progesterone, biological studies 57-91-0, 17.alpha.-**Estradiol** 71-58-9, Medroxyprogesterone acetate 72-33-3, Mestranol 302-22-7, Chlormadinone acetate 427-51-0, Cyproterone acetate 797-63-7, Levonorgestrel 979-32-8, **Estradiol** valerate 5630-53-5, Tibolone 10540-29-1, Tamoxifen 24749-37-9, Estrane 54024-22-5, Desogestrel **58652-20-3**, **Lutenyl** 84371-65-3, RU 486 84449-90-1, Raloxifene
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hormonal **contraceptive**)

L74 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:59650 HCAPLUS
DN 130:134273
TI **Contraceptive** potential of a mifepristone-**nomegestrol acetate sequential** regimen in women
AU Croxatto, Horacio B.; Salvatierra, Ana M.; Fuentealba, Blanca; Massai, Rebeca
CS Inst. Chileno de Medicina Reproductiva (ICMER), Santiago, Chile
SO Hum. Reprod. (1998), 13(12), 3297-3302
CODEN: HUREEE; ISSN: 0268-1161
PB Oxford University Press
DT Journal
LA English
CC 2-3 (Mammalian Hormones)
AB The effectiveness of a **sequential** regimen consisting of mifepristone, 10 mg/day for 15 days, followed by **nomegestrol acetate** (NOMA), 5 mg/day for the next 13 days, for inhibiting ovulation and maintaining regular bleeding cycles was assessed in 10 surgically sterilized volunteers who were followed for one pretreatment and three treated cycles. Hormonal detns. in blood and urine, ovarian ultrasonog., bleeding records in all cycles and an endometrial biopsy taken on day 22-25 of the third treatment cycle were used to monitor the effects of treatment. During treatment, 24 monophasic (no sustained progesterone rise above 12 nmol/l) and six biphasic cycles were recorded. Nine follicular ruptures were detected echog. in these 30 treated cycles, five of which occurred in monophasic cycles. All follicular ruptures occurred on days 1-7 of NOMA treatment. Echog. and endocrine features of ovulatory cycles were both present in only four treated cycles (13.3%). Development of a secretory endometrium was achieved in all cases, but it was always irregular. Regular withdrawal bleeding occurred in all subjects and no adverse reactions were recorded. The ovarian and endometrial effects of this regimen justify testing its **contraceptive** effectiveness in phase 2 clin. trials.
ST mifepristone **nomegestrol acetate** oral **contraceptive** ovulation inhibition ovary endometrium
IT Ovulation
(inhibition; mifepristone **nomegestrol acetate sequential** regimen and its **contraceptive** potential in women)
IT Endometrium (uterus)
Menstruation
Oral **contraceptives**
Ovarian cycle

Ovarian follicle
(mifepristone **nomegestrol acetate** **sequential** regimen and its **contraceptive** potential in women)

IT **58652-20-3, Lutenyl** 84371-65-3, Ru486
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mifepristone **nomegestrol acetate** **sequential** regimen and its **contraceptive** potential in women)

IT **50-28-2, Estradiol**, biological studies 57-83-0, Progesterone, biological studies 9002-67-9, LH
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mifepristone **nomegestrol acetate** **sequential** regimen and its **contraceptive** potential in women)

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(21) van Uem, J; Contraception 1989, V40, P171 HCAPLUS

L74 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:787662 HCAPLUS
DN **130:163331**
TI Coadministration of **nomegestrol acetate** does not diminish the beneficial effects of **estradiol** on coronary artery dilator responses in nonhuman primates (Macaca fascicularis)
AU Williams, J. Koudy; Cline, J. Mark; Honore, Erika K.; Delansorne, Remi; **Paris, Jacques**
CS Department of Comparative Medicine of Wake Forest, University School of Medicine, Winston-Salem, NC, 27157-1040, USA
SO Am. J. Obstet. Gynecol. (**1998**), 179(5), 1288-1294
CODEN: AJOGAH; ISSN: 0002-9378
PB Mosby, Inc.
DT Journal
LA English
CC 2-4 (Mammalian Hormones)
AB Our purpose was to examine the effect of coadministered **nomegestrol acetate** on **estradiol**-induced dilator responses of coronary arteries. In this prospective randomized trial, ovariectomized monkeys were fed a moderately atherogenic diet for 3 mo while being treated with (1) no hormone replacement (control), (2) **estradiol** (1.5 mg/d equiv.) added to the diet, or (3) **estradiol** (1.5 mg/d equiv.) plus **nomegestrol acetate** (3.75 mg/d equiv.) added to the diet. Effects of treatment were measured with anal. of variance. Post hoc analyses were

done by multiple comparison tests with Bonferroni corrections. Constrictor responses of epicardial coronary arteries (measured with quant. angiog.) and decreased coronary blood velocity (measured with Doppler ultrasonog.) to acetylcholine (10-6 mol/L) were less in the **estradiol**-treated monkeys (with or without cotreatment with **nomegestrol acetate**) than in the untreated monkeys. Typical **estrogenic** responses were induced by **estradiol** in the endometrium (i.e., increased proliferation (Ki-67 expression) and increased hormone receptor expression). These effects were antagonized by **nomegestrol acetate**. Although **nomegestrol acetate** has typical progestin-like effects on the uterus, it does not diminish the beneficial effects of **estrogen** on acetylcholine-induced dilator responses of coronary arteries.

ST **nomegestrol acetate estradiol** coronary artery vasodilation

IT Coronary blood flow
(**estradiol** and **nomegestrol acetate** effect on coronary circulation response to acetylcholine in nonhuman primates)

IT Coronary artery
(**nomegestrol acetate** coadministration does not diminish **estradiol** beneficial effects on coronary artery dilator responses in nonhuman primates)

IT 51-84-3, Acetylcholine, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**estradiol** and **nomegestrol acetate** effect on coronary circulation response to acetylcholine in nonhuman primates)

IT **50-28-2, Estradiol**, biological studies
58652-20-3, Nomegestrol acetate
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nomegestrol acetate** coadministration does not diminish **estradiol** beneficial effects on coronary artery dilator responses in nonhuman primates)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L74 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:297313 HCAPLUS

DN 129:49807
TI Insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**
AU Wagner, Janice D.; **Thomas, Michael J.**; Williams, J. Koudy; Zhang, Li; Greaves, Kathryn A.; Cefalu, William T.
CS Department of Comparative Medicine, Bowman Gray School of Medicine, Winston-Salem, NC, 27157-1040, USA
SO J. Clin. Endocrinol. Metab. (1998), 83(3), 896-901
CODEN: JCEMAZ; ISSN: 0021-972X
PB Endocrine Society
DT Journal
LA English
CC 2-4 (Mammalian Hormones)
AB The authors have previously shown that medroxyprogesterone acetate (MPA), either alone or **combined** with conjugated equine **estrogens** (CEE), significantly decreased insulin sensitivity (SI), compared with both untreated controls and those treated with CEE alone. The purpose of this study was to det. the effects of **estradiol** (E2), with and without **nomegestrol acetate** (NA; a potent progestin that lacks androgenic activity), on SI and arterial antioxidant activity, as detd. by F2-isoprostanes. Thirty-six adult female cynomolgus monkeys (Macaca fascicularis) were ovariectomized and fed a moderately atherogenic diet, with one of the following three treatments added to the diet, for 12 wk: (1) no treatment (control); (2) E2; or (3) continuous **combined** E2 + NA. SI and glucose effectiveness were assessed by the frequently sampled i.v. glucose tolerance test using a third-phase insulin infusion after 10 wk of treatment. Cholesterol content and F2-isoprostanes were measured in the thoracic aorta after 12 wk of treatment. E2 treatment resulted in a significantly greater SI, compared with control or E2+NA-treated monkeys (10.03 vs. 35 and 6.49 .times. 10-4 min-1 .mu.U-1mL). In contrast to the authors' studies of CEE and MPA, E2+NA treatment, though reducing the SI below that of the E2 group, did not reduce the SI below that of control monkeys. As expected, the short period of treatment resulted in no significant differences in aortic cholesterol content. There was no treatment effect on total F2-isoprostanes (representing F2-isoprostane formation caused primarily by autoxidn.), suggesting minimal antioxidant activity. However, there was a treatment difference in the prostaglandin F2.alpha. (PGF2.alpha.) isomer (a prostaglandin (PG) isomer formed by both autoxidn. of arachidonate and cyclooxygenase activity). PGF2.alpha. concns. were 32% lower with E2 treatment, compared with controls, and 36% lower, compared with E2+NA treatment (0.48 vs. 71 and 0.75), suggesting differences in PG synthesis between hormone treatments. In conclusion, NA, a progestin without androgenic activity, may still affect some cardiovascular risk factors differently than **estrogen**-only therapy. However, it seems to be less detrimental than MPA.
ST insulin cardiovascular risk **estradiol nomegestrol** monkey
IT Prostaglandins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(F2-isoprostanes; insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)
IT Antioxidants
Artery
Atherosclerosis
Cardiovascular agents
Macaca fascicularis
Thoracic aorta
(insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)
IT Blood cholesterol
Low-density lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)

IT **50-28-2, Estradiol**, biological studies
58691-88-6, Nomegestrol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)

IT 551-11-1, PGF2.alpha.
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)

IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(tolerance; insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with **estradiol** alone or **combined** with **nomegestrol acetate**)

L74 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:239116 HCAPLUS
DN 128:312905
TI Pharmaceutical **composition** consisting of an **estrogen** and a progestogen
IN Lanquetin, Michel; **Paris, Jacques**; **Thomas, Jean-Louis**
PA Laboratoire **Theramex**, Monaco; Lanquetin, Michel; Paris, Jacques; Thomas, Jean-Louis
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM A61K031-57
ICS A61K031-57; A61K031-565
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9815279	A1	19980416	WO 1997-FR1792	19971008 <--
	W: AU, BR, CA, CN, CU, CZ, HU, ID, IL, JP, KR, MG, MX, NO, NZ, PL, RO, RU, SG, SK, TR, US, VN, YU				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	FR 2754179	A1	19980410	FR 1996-12239	19961008 <--
	FR 2754179	B1	19981224		
	AU 9746273	A1	19980505	AU 1997-46273	19971008 <--
	ZA 9709011	A	19980603	ZA 1997-9011	19971008 <--
	BR 9712274	A	19990831	BR 1997-12274	19971008 <--
	EP 956022	A1	19991117	EP 1997-944940	19971008 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1239893	A	19991229	CN 1997-180380	19971008 <--
	NO 9901593	A	19990607	NO 1999-1593	19990331 <--
	KR 2000048981	A	20000725	KR 1999-703032	19990408 <--
PRAI	FR 1996-12239	A	19961008 <--		
	WO 1997-FR1792	W	19971008 <--		

AB The invention concerns the field of chem. therapy and more particularly

the field of pharmaceutical hormonal technique. More precisely it concerns novel pharmaceutical hormonal compns. characterized in that they are formed by an **estrogen**-progestogen combination assocd. or mixed with 1 or several nontoxic, inert and excipients, for oral administration. The combined assocn. can be prescribed continuously or intermittently, for producing a compn. for treating **estrogenic** deficiencies, preventing osteoporosis and cardiovascular diseases in menopausal women, or still for blocking **ovulation** in a woman during the period of **ovarian** activity. Thus, tablets contained **estradiol** 1.5, **nomegestrol acetate** 2.5, Avicel PH-102 22.4, lactose 60, PVP 8.4, colloidal silica 1.2, glycerol palmitostearate 3.6, and dye 0.4 mg. The effectiveness of this combination in the treatment of diseases in menopausal women was demonstrated.

ST **estrogen** progestogen pharmaceutical

IT Cardiovascular diseases
Menopause
Osteoporosis
Ovulation
(pharmaceutical compn. consisting of an **estrogen** compd. and of a progestogen)

IT Progestins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. consisting of an **estrogen** compd. and of a progestogen)

IT **Estrogens**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. contg. **estrogen** and progestogen)

IT **50-28-2, Estradiol**, biological studies **50-28-2D**
, Estradiol, derivs. 979-32-8, **Estradiol** valerate
58652-20-3, Nomegestrol acetate
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. consisting of an **estrogen** compd. and of a progestogen)

L74 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:229672 HCAPLUS
DN **126:272509**
TI Impact of percutaneous **estradiol** gels in postmenopausal hormone replacement therapy on clinical symptoms and endometrium
AU Foidart, Jean-Michel; Beliard, Aude; Hedon, Bernard; Ochsenbein, Edith; Bernard, Anne-Marie; Bergeron, Christine; **Thomas, Jean-Louis**
CS Laboratory of Biology, Centre Hospitalier du Bois de l'Abbaye, University of Liege and Department of Obstetrics and Gynaecology, Seraing, Belg.
SO Br. J. Obstet. Gynaecol. (**1997**), 104(3), 305-310
CODEN: BJOGAS; ISSN: 0306-5456
PB Blackwell
DT Journal
LA English
CC 2-4 (Mammalian Hormones)
AB Our objective was to compare the effects on endometrium, climacteric symptoms and the menstrual cycle, and the clin. and biol. tolerance of two percutaneous **estradiol** gels used as hormone replacement therapy. Two-hundred and fifty-four women with an intact uterus and who had experienced a natural menopause received either Oestrogel(n = 126) or Estreva a new formulation of **estradiol** gel (n = 128), (1.5 mg of **estradiol**/day) for the 24 first days of each calendar month during six consecutive months. **Nomegestrol acetate** (**Lutenyl**), a norprogesterone deriv., was administered (5 mg/day) from day 11 to day 24 of each **estradiol** cycle. Examn. of endometrial biopsies taken before treatment and between days 18 and 24 of the last treatment cycle, climacteric symptoms assessed using a modified Kupperman index, control of menstrual cycle evaluated by diary cards, and clin. and biol. tolerance. Both treatments lowered the frequency and intensity of hot flushes and the global Kupperman index. 96% Of the

cycles were followed by withdrawal bleeding. Breakthrough bleeding or spotting resulted in premature discontinuation of treatment in one volunteer. Mastodynia occurred in 20 women and contributed to the premature termination of treatment in three of them. Endometrial biopsies taken at the end of treatment showed identical histologies in both groups, with a secretory pattern in the majority of women, and absence of hyperplasia. This trial confirmed that, when the two **estradiol** gels tested were administered cyclically with **nomegestrol acetate** to postmenopausal women, they were well tolerated, effective and suitable for the treatment of **estrogen** deficiency syndrome.

ST **estradiol** endometrium postmenopause hormone replacement therapy

IT Endometrium (uterus)
Postmenopause
(impact of percutaneous **estradiol** gels in postmenopausal hormone replacement therapy on clin. symptoms and endometrium in humans)

IT Hormones (animal), biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(replacement therapy; impact of percutaneous **estradiol** gels in postmenopausal hormone replacement therapy on clin. symptoms and endometrium in humans)

IT **50-28-2**, **Estradiol**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(impact of percutaneous **estradiol** gels in postmenopausal hormone replacement therapy on clin. symptoms and endometrium in humans)

L74 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:226799 HCAPLUS
DN **126:216684**
TI Novel hormonal medicaments and use thereof for correcting **estrogen** deficiencies
IN Lanquetin, Michel; **Paris**, **Jacques**; **Thomas**, **Jean-Louis**
PA Laboratoire **Theramex**, Monaco; Lanquetin, Michel; Paris, Jacques; Thomas, Jean-Louis
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM A61K031-57
ICI A61K031-57, A61K031-565
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9704784	A1	19970213	WO 1996-IB754	19960729	<--
	W: AU, BR, CA, CN, CZ, FI, HU, IL, JP, KR, MX, NO, RU, SG, US, VN					
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	FR 2737411	A1	19970207	FR 1995-9364	19950801	<--
	FR 2737411	B1	19971017			
	CA 2201368	AA	19970213	CA 1996-2201368	19960729	<--
	AU 9663674	A1	19970226	AU 1996-63674	19960729	<--
	AU 722355	B2	20000727			
	EP 783310	A1	19970716	EP 1996-923018	19960729	<--
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	CN 1167438	A	19971210	CN 1996-191100	19960729	<--
	BR 9606549	A	19980623	BR 1996-6549	19960729	<--
	JP 10507207	T2	19980714	JP 1996-507406	19960729	<--
	ZA 9606545	A	19970508	ZA 1996-6545	19960801	<--
	NO 9701449	A	19970530	NO 1997-1449	19970326	<--

US 5891867 A 19990406 US 1997-817329 19970424 <--
PRAI FR 1995-9364 A 19950801 <--
WO 1996-IB754 W 19960729 <--
AB A trisequential, oestroprogestogen hormonal combination characterized in that it comprises unit doses contg. only one **estrogen**, unit doses contg. a combination of one **estrogen** and one progestogen, and unit doses contg. only one carrier. The trisequential delivery mode aims at compensating functional disorders caused by menopausal or pre-menopausal **hypoestrogenism**. Formulation of 1.5 mg 17.beta.-**estradiol** tablets and 2.5 mg **nomegestrol acetate** tablets are disclosed. The efficacy of tablets in treatment of hot flashes in menopausal women are reported.
ST pharmaceutical tablet **estrogen** deficiency progestogen
IT Glycerides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C16-18; novel hormonal medicaments for correcting **estrogen** deficiencies)
IT **Estrogen** deficiency
Menopause
Tablets (drug delivery systems)
(novel hormonal medicaments for correcting **estrogen** deficiencies)
IT **Estrogens**
Progestins
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel hormonal medicaments for correcting **estrogen** deficiencies)
IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst.; novel hormonal medicaments for correcting **estrogen** deficiencies)
IT **50-28-2**, 17.beta.-**Estradiol**, biological studies
35380-71-3, **Estradiol** hemihydrate **58652-20-3**, **Nomegestrol acetate**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel hormonal medicaments for correcting **estrogen** deficiencies)
IT 67-63-0, Isopropyl alcohol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(novel hormonal medicaments for correcting **estrogen** deficiencies)
IT 63-42-3, Lactose 7631-86-9, Silica, biological studies 9003-39-8, Pvp 9003-39-8D, Pvp, crosslinked
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel hormonal medicaments for correcting **estrogen** deficiencies)

L74 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:746706 HCAPLUS
DN **126:42825**
TI The antigonadotropic activity of progestins (19-nortestosterone and 19-norprogesterone derivatives) is not mediated through the androgen receptor
AU Couzinet, Beatrice; Young, Jacques; Brailly, Sylvie; Chanson, Philippe; **Thomas, Jean Louis**; Schaison, Gilbert
CS Service Endocrinologie Maladies Reproduction, Hop. Bicetre, Kremlin, 94275, Fr.
SO J. Clin. Endocrinol. Metab. (**1996**), 81(12), 4218-4223
CODEN: JCEMAZ; ISSN: 0021-972X
PB Endocrine Society
DT Journal
LA English
CC 2-4 (Mammalian Hormones)
AB To further study the mechanism of the antigonadotropic activity of

progestins, the effects of a 19-nortestosterone deriv., norethisterone acetate (NETA), and a 19-norprogesterone deriv., **nomegestrol acetate** (NOMA), were compared. The aim was to assess whether their action is exerted via the androgen receptor. Ten healthy postmenopausal women were treated for five monthly periods of 24 days sepd. by 10 days in a randomized crossover design. Transdermal **estradiol**, Estraderm TTS (25 .mu.g; one patch every 3 days), was given from days 1-24 during the five periods. On the last 12 days, of each **estradiol** treatment, they all received a placebo, NOMA (5 mg/day), NOMA in assocn. with the nonsteroidal antiandrogen, flutamide (FLU; 250 mg, twice a day), NETA (10 mg/day), or NETA plus FLU. On the other hand, three castrated patients with complete androgen insensitivity (CAI) received NOMA and NETA for two periods of 12 days sepd. by 3 wk. In postmenopausal women, the effects of NOMA and NETA on metabolic parameters were studied. Only NETA decreased high d. lipoprotein cholesterol. Plasma LH, FSH, and **estradiol** were measured during each treatment period. A significant decrease in mean plasma LH and FSH levels and their responses to exogenous GnRH was obsd. with NOMA and NETA treatments compared to placebo. The pulsatile frequency, but not the amplitude, of LH was significantly decreased during both treatments. Interestingly, the effects of both progestins on gonadotropins were not antagonized by FLU administration. In the patients with CAI, the pulsatile study of gonadotropins was performed before and on day 12 of NOMA and NETA treatments. As in postmenopausal women, both progestins induced similar decreases in LH and FSH. In conclusion, a 19-nortestosterone deriv., NETA, and a 19-norprogesterone deriv., NOMA, have similar antigonadotropic activities. This effect, not antagonized by FLU and obsd. in patients with CAI, is not mediated via the androgen receptor. The absence of deleterious effects of 19-norprogesterone derivs. on metabolic parameters should favor the therapeutic use of these compds.

ST antigonadotropic nortestosterone norprogesterone androgen receptor

IT Postmenopause
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT Progestins
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT Androgen receptors
High-density lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT Androgen insensitivity
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT 9034-40-6, LH-RH 13311-84-7, Flutamide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT **50-28-2, Estradiol**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

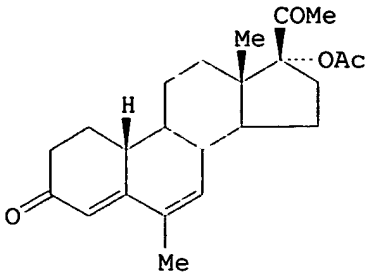
IT 51-98-9, Norethisterone acetate **58652-20-3, Nomegestrol acetate**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

IT 57-88-5, Cholesterol, biological studies 9002-67-9, LH 9002-68-0, FSH

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antigonadotropic activity of progestins is not mediated by androgen receptor)

L74 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:725440 HCAPLUS
TI Subdermal **contraceptive** implants
AU Peralta, Octavio; Diaz, Soledad; Croxatto, Horacio
CS Instituto Chileno de Medicina Reproductiva, Santiago, Chile
SO J. Steroid Biochem. Mol. Biol. (1995), 53(1-6), 223-6
CODEN: JSBBEZ; ISSN: 0960-0760
DT Journal
LA English
AB Subdermal **contraceptive** implants involve the delivery of a steroid progestin from polymer capsules or rods placed under the skin. The hormone diffuses out slowly at a stable rate, providing **contraceptive** effectiveness for 1-5 yr. The period of protection depends upon the specific progestin and the type of polymer. Advantages of progestin implants include long term **contraceptive** action without requiring the user's or provider's attention, low dose of highly effective **contraception** without the use of **estrogen**, and fertility is readily reversible after the removal of implants. The levonorgestrel implant Norplant R system is the only one that has been approved for distribution. The **contraceptive** efficacy of Norplant is the highest obsd. amongst the most effective methods with an annual pregnancy rate of 0.2 during the first and second year and 1.1 on the fifth year. Menstrual problems are the main reason for the discontinuation of Norplant and 9% of women stopped using it during the first year of treatment. Other implants are still under development trying to simplify the method by reducing the no. of units and to introduce other progestins that may minimize side effects. Norplant-2 was designed to release the same dose of progestin from only two covered rods. Evaluation of 1400 women enrolled, indicates that voer 2 yr the cumulative pregancy rate is below 0.5 per 100 women. There are three single implants under development: Nestorone, 3-Keto-desogestrel and **Uniplant** that are expected to be effective for 1-2 yr. Phase II clin. trials with Nestorone have been completed and no pregnancies have been obsd. in 1570 woman-months of use. Bleeding irregularities occurred in 20-30% of the women but there were only four terminations because of bleeding problems. A multricentric study is ongoing with a newly designed 3-keto-desogestrel implant named Implanon, which releases approx. 60 Mg/day of the hormone. The objectives of this study are to assess **contraceptive** efficacy, safety and acceptability of Implanon. Another multricentric study is ongoing with **Uniplant**, which releases **nomegestrol acetate** with a duration of action for only 1 yr. The objectives of the trial are to study the endocrine profile of **Uniplant** users and to evaluate the efficacy and acceptability of the method.

L74 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 1987:149754 HCAPLUS
DN **106:149754**
TI Effects of progesterone and **nomegestrol acetate** on rabbit endometrial epithelium. Scanning-electron-microscopic study
AU **Paris, J. M.**; Mrena, E.; Lanquetin, A.; Marchal, G. M.; Thevenot, R.
CS Lab. **Theramex**, Monaco, 98000, Monaco
SO J. Pharmacol. **(1986)**, 17(4), 508-14
CODEN: JNPHAG; ISSN: 0021-793X
DT Journal
LA French
CC 2-4 (Mammalian Hormones)
GI



I

AB Priming of immature rabbits with **estradiol** [50-28-2] followed by injection of progesterone [57-83-0] (2-12.5 mg) s.c. for 5 days resulted in changes in endometrial morphol. as detected by SEM which were similar to the changes occurring in postmenopausal women on estroprogestative therapy. Similar changes were obsd. when **nomegestrol acetate** (I) [58652-20-3] (0.25-12.5 mg, orally) was substituted for progesterone. Thus, the 19-norprogesterone deriv. displayed similar activity to the parent compd.

ST uterus morphol progesterone **nomegestrol**; endometrium morphol progesterone **nomegestrol**

IT Uterus
(endometrium, epithelium, morphol. of, **estradiol** and **nomegestrol** and progesterone effect on)

IT Menopause
(post-, **estradiol** and **nomegestrol** and progesterone effect on endometrium morphol. in relation to)

IT 57-83-0, Progesterone, biological studies
RL: BIOL (Biological study)
(uterus endometrium morphol. response to **estradiol** and, **nomegestrol** in comparison with)

IT **58652-20-3, Nomegestrol acetate**
RL: BIOL (Biological study)
(uterus endometrium morphol. response to **estradiol** and, progesterone in comparison with)

IT **50-28-2, Estradiol**, biological studies
RL: BIOL (Biological study)
(uterus endometrium morphol. response to **nomegestrol** and progesterone and)

=> fil reg
FILE 'REGISTRY' ENTERED AT 11:55:27 ON 15 MAR 2002

STRUCTURE FILE UPDATES: 13 MAR 2002 HIGHEST RN 400796-85-2
DICTIONARY FILE UPDATES: 13 MAR 2002 HIGHEST RN 400796-85-2

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the

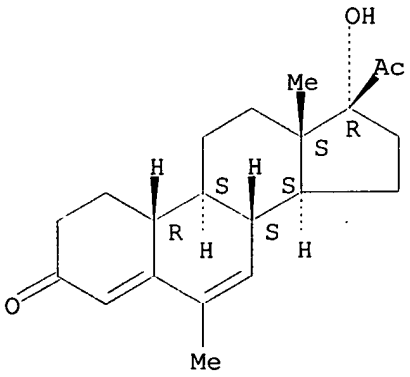
CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

=> d ide can l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 58691-88-6 REGISTRY
CN 19-Norpregna-4,6-diene-3,20-dione, 17-hydroxy-6-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Nomegestrol**
CN TX 071
FS STEREOSEARCH
MF C21 H28 O3
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PROMT, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

23 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
23 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:15686

REFERENCE 2: 134:316159

REFERENCE 3: 134:157767

REFERENCE 4: 133:350205

REFERENCE 5: 133:350135

REFERENCE 6: 133:330062

REFERENCE 7: 133:330061

REFERENCE 8: 133:276797

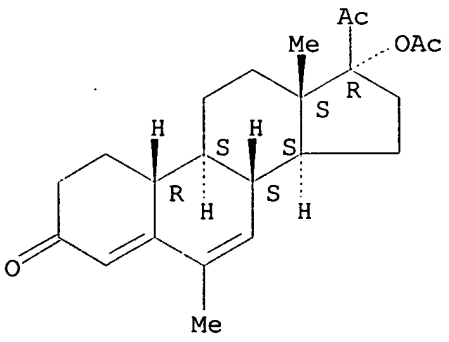
REFERENCE 9: 132:44984

REFERENCE 10: 131:262597

=> d ide can l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 58652-20-3 REGISTRY
CN 19-Norpregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 6-Methyl-17.alpha.-acetoxy-.DELTA.6-19-norprogesterone
CN Lutenyl
CN **Nomegestrol acetate**
CN Surplant
CN TX 066
CN Uniplant
FS STEREOSEARCH
MF C23 H30 O4
LC STN Files: ADISINSIGHT, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMLIST, CIN, DDFU, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

65 REFERENCES IN FILE CA (1967 TO DATE)
66 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:857

REFERENCE 2: 136:799

REFERENCE 3: 135:327515

REFERENCE 4: 135:298911

REFERENCE 5: 134:316160

REFERENCE 6: 134:316159

REFERENCE 7: 134:173207

REFERENCE 8: 134:51472

REFERENCE 9: 134:37255

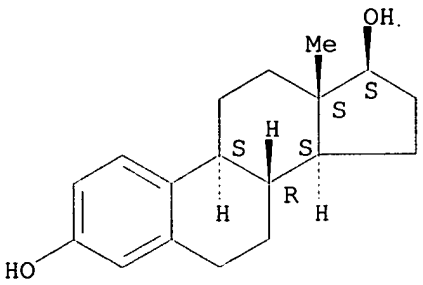
REFERENCE 10: 134:36648

=> d ide can l5

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 50-28-2 REGISTRY
CN Estra-1,3,5(10)-triene-3,17-diol (17.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Estradiol (8CI)**
OTHER NAMES:
CN (+)-3,17.beta.-Estradiol
CN .beta.-Estradiol
CN 13.beta.-Methyl-1,3,5(10)-gonatriene-3,17.beta.-ol
CN 17.beta.-Estradiol
CN 17.beta.-Oestradiol
CN 3,17-Epidihydroxyestratriene
CN 3,17.beta.-Dihydroxyestra-1,3,5(10)-triene
CN 3,17.beta.-Estradiol
CN Aerodiol
CN Altrad
CN Aquadiol
CN Bardiol
CN Beta-estradiol
CN Climaderm
CN Climara
CN Compudose
CN Compudose 200
CN Compudose 365
CN Corpagen
CN Dermestril
CN Dihydrofollicular hormone
CN Dihydrofolliculin
CN Dihydromenformon
CN Dihydrotheelin
CN Dihydroxyestrin
CN Dimenformon
CN Diogyn
CN Diogynets
CN Divigel
CN E 2
CN Encore
CN Epiestriol 50
CN Estra-1,3,5(10)-triene-3,17-diol, (17.beta.)-
CN Estra-1,3,5(10)-triene-3,17.beta.-diol
CN Estrace
CN Estraderm
CN Estraderm TTS
CN Estraderm TTS 50
CN Estraldine
CN Estroclim 50
CN Estrogel
CN Estrovite
CN Evorel
CN Femestral

CN Femogen
CN Follicyclin
CN Ginosedol
CN Gynergon
CN Gynoestryl
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS STEREOSEARCH
MF C18 H24 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43197 REFERENCES IN FILE CA (1967 TO DATE)
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43256 REFERENCES IN FILE CAPLUS (1967 TO DATE)
12 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:172889

REFERENCE 2: 136:172796

REFERENCE 3: 136:172603

REFERENCE 4: 136:166733

REFERENCE 5: 136:166686

REFERENCE 6: 136:166058

REFERENCE 7: 136:165365

REFERENCE 8: 136:165337

REFERENCE 9: 136:165223

REFERENCE 10: 136:165188